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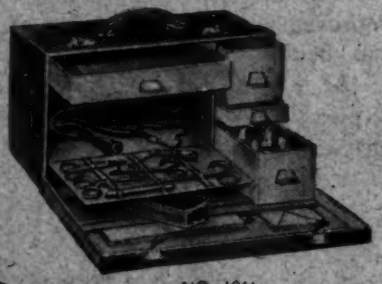

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 13 1952

USE OF RADIOACTIVE PHOSPHORUS IN MAPPING BRAIN TUMOURS AT OPERATION

BY

T. P. MORLEY, F.R.C.S.
Senior Registrar

AND

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During the last thirty years or so new and mechanical techniques have been introduced into neurosurgery to amplify or verify the information obtained by classical clinical procedures. They were needed because, however excellent the observations, there were often doubts in interpretation. First came ventriculography, which helped greatly in location but which often brought important dangers into the management of a case that a surgeon would have preferred to avoid had alternatives existed. Next came angiography, which when successful gave not only the tumour site but often clues to its histological nature.

Attempts have recently been made to improve on both of these diagnostic aids—by the use, for instance, of the reflection or attenuation of ultrasonic waves passed through the head in the hope that the pattern of the ventricles would emerge (Ballantine *et al.*, 1950). But the most useful of the new techniques lies in the field of the isotopes, a subject well summarized in a recent annotation in the *British Medical Journal* (1952). Brain tumours pick up chemical substances in much greater quantity than does the normal grey or white matter, and some isotopes penetrate in only the smallest quantities into the cerebrospinal fluid. This affinity for chemical substances seems to depend on the cellularity of the tumour rather than on the immaturity or number of the tumour's blood vessels. The substances used so far have been radioactive phosphorus (P^{32}), potassium (K^{42}), di-iodofluorescein (I^{131}), and manganese ($_{25}Mn^{52}$ and $_{25}Mn^{54}$). After injecting radioactive iodine compounds or a manganese salt (the latter a positron-emitter) it has been found possible to pick up the emanations through the intact skull by means of scintillators which are fifty times as efficient as the standard Geiger–Müller counter. Davis *et al.* (1950), Moore and his co-workers (1950), and Brownell and Sweet (1952, personal communication) have all had some success with this method. The advantages of such procedures over ventriculography and angiography are self-evident, though neither of these older methods is at all likely to become obsolete. Midline tumours, those of the third ventricle and thalamus, and tumours of the pineal region and brain-stem are not such as can be satisfactorily demonstrated by these newer means, while some sparse-celled tumours may give ambiguous results. But certainly it would be an advance if we could tell by a bloodless and harmless method that a tumour is present, even though the details had still to be worked out by other ways.

The use that we have made of P^{32} is quite different and would not lose its usefulness even if the gross location of the tumour had already been made by means of radioactivity. We have followed closely the plan laid down by Selverstone, Sweet, and Robinson (1949) and Selverstone, Solomon, and Sweet (1949). The object is to map the extent of tumour, subcortical or otherwise, after its site has been exposed, or to pin-point its location in order that a successful biopsy may be made.

Technique

One millicurie of P^{32} is injected intravenously the evening before operation—a period of approximately 12 hours. The dose of P^{32} and the time of injection are immaterial provided that the concentration of beta emissions from normal brain is great enough to be recorded and that the dose of P^{32} is not so large as to harm the patient. We have tried to keep the dose and time interval between injection and recording standard so that the readings of the rate of beta emission taken at operation are comparable in all cases. Lately, however, we have found that P^{32} is concentrated in a significant amount in tumour within minutes of the injection. In three such cases the tumours had been exposed before the injections were made. This is in line with similar findings by Easson and Gilbert (1951, personal communication), who studied the rate of uptake of the isotope in different tissues, including breast cancer. At operation the modified Geiger–Müller probe counter—designed by Selverstone and Robinson and described by Robinson and Peterson (1948) (Fig. 1)—is used to detect the tumour by picking up the beta particles emanating from it when the probe is inserted into or very close to the tumour.

The detailed description of the apparatus is beyond the scope of this article, but it is necessary to mention its essential features. P^{32} is a pure beta-emitter, and this is why it was originally chosen by Selverstone in this work, for its emission is uncontaminated by gamma radiation. The range of the beta particles of phosphorus in normal white matter is only 5 to 8 mm. This short range is an essential factor for the accurate recognition of the position of a tumour. The probe is made of thin stainless steel (cathode) and is marked

in centimetres, but the part of the tube that contains within it the "active" anode is situated near the probe's tip, and it is therefore only from this point that beta emissions are picked up and recorded. The probe is connected by a plastic insulated flexible attachment to a combined amplifier and count-rate meter that records by both dial and loudspeaker. The latter is an important addition to the instrument, for it enables the surgeon to be aware of the activity of the tissue he is probing without taking his eye off the field of operation. We cannot agree with Davis (1951) in the criticism he levelled at the Selverstone probe counter on the grounds that its fragility and instability make it impracticable for routine theatre work. It will not withstand rough handling, but there is no reason why it should receive it. The life of this probe model is limited to about ten million counts. Owing to the difficulty of replacement the counter was used only when it had a definite role in the management of a case.

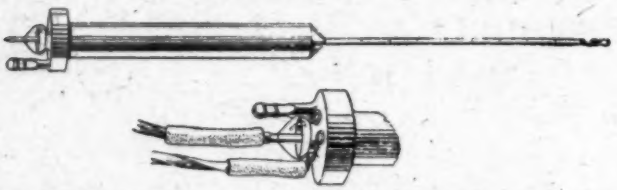

FIG. 1.—Line drawing of the counter. The dark area near the tip represents the sensitive part of the probe. The probe is marked in centimetres. The method of attachment of the leads is shown.

Apart from the information this method can give in locating a tumour, it is a simple and practicable technique that can be used in any operating theatre. No extra assistant is required, and the precautions to be taken in handling the P^{32} are little different from familiar aseptic practice. No special knowledge of electronics is needed in the interpretation of the results. The equipment uses the mains supply of electricity. It is portable and unobtrusive, and, by modern standards, cheap (the whole outfit costs about £150). The probe can be sterilized by immersion in lysol or by autoclaving at 120° C. for five minutes, and the leads suffer no harm from boiling. The probe has an external diameter of slightly more than 2 mm., which is the dimension of brain cannulae in everyday use.

Discussion

Even with the help of P^{32} the surgery of the gliomas remains disappointing because of their tendency to invade basal structures and because such invasion is already present in many patients by the time they become aware that something is wrong. This is not universally true, but it is very often the case. It is possible to see the place where gliomas fade into normal brain, but sometimes the observer cannot define the boundary very narrowly. It would be an advantage if the absolute boundary could be detected by the radioactivity of a narrow fringe containing but few cells. This would call for a degree of sensitivity beyond anything yet available. The objection may be made that even if one knew to a millimetre it would make no practical difference for the reason already mentioned—invasion of functionally vital areas. But everything that gives greater precision and immediate knowledge of tumour extent must be welcomed. Future probe counters may fulfil this demand. The present type will detect a cellular piece of tumour but will not make known the few scattered cells sufficient to ensure recurrence. It might do that service better with larger doses of P^{32} (up to 2 or 3 mc.), but we have been content as a rule with recognition of the main tumour mass, and with the naked eye to define the boundary. We should add that in one case in which a meningioma of the inner and middle thirds of the sphenoidal wing had been removed the counter discovered an unsuspected nubbin of tumour that had been left behind under the frontal lobe. Our uses of P^{32} can best be summarized as follows.

(1) *Recognition of Tumour Tissue for Biopsy.*—Perhaps the most useful application of the method is in the taking of biopsy specimens by puncture and aspiration along a cannula introduced through a burr-hole. Every experienced neurosurgeon knows how uncertain the burr-hole biopsy can be, yet by confirmation of histological structure a tedious and useless operation can be avoided. This is particularly true, as everyone knows, of malignant gliomas and secondary tumours, especially in aphasic and hemiplegic patients. Such a tumour can often be felt with the cannula, but sometimes it is far from certain that a satisfactory specimen has been obtained. By exploring with the probe counter one can make sure that a cellular part of the tumour has been found. The brain cannula can then be passed to the same depth and in the same direction as the probe with confidence that tissue extracted from that situation will contain tumour cells. Even more gratifying confirmation is obtained when the radioactivity of the tiny fragment removed confirms the fact immediately that a specimen of tumour has indeed been secured. Out of 15 burr-hole biopsies conducted in this way 14 gave the information sought. In Fig. 2 the findings in one such case have been graphically recorded. The fall in count rate as the probe enters the white matter is well shown. The fall may not occur until a depth of 2 cm. or so has been reached if the probe is in contact with the buried grey matter surrounding a sulcus or fissure. The cortical counts are relatively low and are in marked contrast with the rise that occurs when a cellular tumour is penetrated.

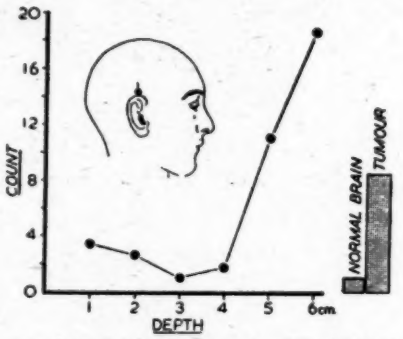

FIG. 2.—Detection through a burr-hole of active tumour situated at considerable depth. Biopsy: secondary carcinoma. Cortex invariably shows a slightly greater activity than white matter. The stippled blocks represent the activity of biopsy fragments of normal brain and tumour.

(2) *Mapping the Lay-out of a Subcortical Tumour.*—When a direct attack is to be made on a tumour lying subcortically it is valuable in planning the incision into the brain if one can discover the exact depth at which the tumour begins to influence the counter. The operator knows that the probe is touching it, and by sinking the counter at several points he can map out the lie of the tumour. Further, it can be discovered, by probing before excision is attempted, whether the tumour is accessible (Fig. 3) or extends into regions that cannot be removed—for instance, the motor area—or whether, again, in frontal lesions, tumour activity can be recognized in the opposite hemisphere, rendering a unilateral lobectomy fruitless. Such steps as these are helpful in the surgical attack. Selverstone and White (1951) have shown by comparison between isotope maps at operation and the verified extent of the tumour at post-mortem examination how closely the prediction tallies with the facts.

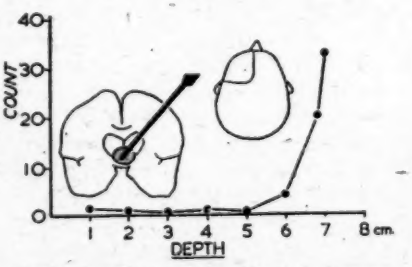

FIG. 3.—Deep left frontal tumour suspected. Probing with the counter revealed active tumour filling the third ventricle. Operation terminated.

We have spoken of tracing a tumour in terms of large extent. There is another side to it; the discovery that a tumour is smaller than had been thought. Thus, by passing

the counter through a tumour, a sudden fall in registration of beta particles indicates that the probe is out into normal white matter on the far side (Fig. 4). This is very valuable information, and an encouragement to radical surgery.

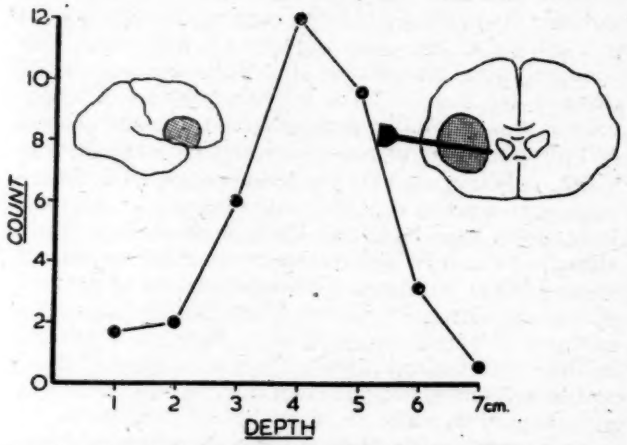

FIG. 4.—At operation a tumour (astrocytoma) was seen on the surface of the convexity of the brain. Its deep extent was mapped with the counter; radical removal was undertaken

(3) *Scanning the Bed from which a Tumour has been Removed.*—We are doubtful of the value of the counter for this purpose in its present degree of sensitiveness. We have had only one case of glioma in which completely negative responses were obtained after radical excision. It is too soon yet to say how reliable the information was, since the operation was done only a year ago. We have not used the counter for cerebellar gliomas, as the extent of these tumours can usually be accurately recognized by vision, and when they do fade out it is usually because they are invading the medulla oblongata or pons, where they could not be pursued in any case.

(4) *Negative Information.*—In only four cases did we obtain no reply on puncture. One of these was a diffuse and very slow-growing basal ganglion glioma. It is probable that owing to the existence of a large hydrocephalus the probe never entered into tumour tissue. In another, proof was obtained at necropsy that the lesion was a vascular one in spite of a history strongly suggesting neoplasm. In two others, although tough resistance indicated that the probe was certainly in a tumour, the counts were lower than even in the neighbouring white matter. Biopsy proved that the tissue was neoplastic; both were fibrillary astrocytomas.

Material

Our series is a small one. We have used the probe in 37 cases out of a total of over 200 tumours operated on during the same period. But the method had already proved its value, and we used it only when we thought that the information it could give was unobtainable by any other means. "True-negative" responses have already been alluded to. "False-negative" recordings are obtained when the probe is not directed into or near the tumour. Small deeply situated tumours may be missed in this way, and it is plain that good location is required by other means before the probe is used. A small tumour situated at a depth of, say, 6 cm. may escape detection by the probe passing to either side of it. At that depth a small change of direction of the probe will result in a considerable change of position of its tip, and there is obviously a limit to the number of times the probe may be passed before the brain suffers damage. With some tumours, particularly astrocytomas, the radioactivity may not be high. We assumed that the lowest significant count rate was twice that produced by probing normal cortex, and that such a difference indicated pathological activity; the difference was usually very much greater—up to 50 times more. A "false-positive" recording may be encountered when the cavity left after removal of a tumour is scanned. There may be no tumour remaining except at one point, yet the emissions from that piece may be picked up on the far wall of the cavity because the particles travel a considerable distance in air. The tip of the probe must be buried in brain before a positive reading is accepted as the true one.

It is not possible to make a pathological diagnosis from the activity of the tumour. Meningiomas, glioblastomas, and secondary carcinomas emit beta particles at comparable rates and the differences in a small series are not significant. Reduced activity is found in areas of gross central necrosis in malignant tumours. The less vascular and better-differentiated astrocytomas, however, appear not to take up the isotope with such facility. In this respect astrocytomas behave in the same way when di-iodofluorescein is presented to them in the blood stream. The figures for the tumours in our series are set out in the Table. Counts in normal brain vary within a narrow range from one person to another. The count of normal white matter must be taken in each case in order to compare it with the count obtained from tumour. The ratio between the two figures gives the "differential count."

	No. of Cases	Range of Differential Counts	Average Differential Count
Meningiomas	7	10–40	22
Secondary carcinomas ..	5	6–50	18
Glioblastomas	8	6–50	17
Astrocytomas	11	1–12	6

Much discussion has taken place on the subject of which component in a tumour is responsible for the uptake of the isotope—the tumour cells or the newly formed capillaries. One thing is certain: increased activity is not due simply to increased blood supply, for then the highest recordings would be found in blood alone, and that is not so. It seems that activity increases with the metabolism of the tissue, and in this all cell elements share. Nor is this increased activity peculiar to brain tumours, for those in other parts of the body have the same property. A cerebral inflammatory lesion may occasionally show it: one case in our series is of particular interest. Exploration of a suspected frontal tumour with the probe indicated an area low in the frontal pole of very greatly increased radioactivity. A circumscribed reddish mass some 4 cm. in diameter was removed, and was proved histologically to be an old abscess. The inflammatory focus had not reached the final stage of scarring and gliosis, but was in effect a small pyogenic granuloma with an active thick wall.

The term "blood–brain barrier" can be misleading in so far as it suggests that there is some unique property of the capillary endothelium in the brain: it is the chemical nature of the brain tissue in which the capillary lies that determines what shall go through the vessel wall. Certainly the isotope is concentrated in abnormally large amounts in cerebral tumour and in inflammatory lesions, but this is a property not confined to such conditions in the brain alone. A rich endowment with blood vessels offers a quantitatively greater opportunity for the tumour cells to exchange phosphorus.

Studies with tracer elements have shown that substances injected into the blood stream are distributed and concentrated in some normal organs—for example, liver, spleen, thyroid, bone marrow—with astonishing rapidity to serve their high metabolic requirements. It is for this reason that P^{32} could not be used in doses sufficient to kill a tumour, since it will damage the liver and other vital organs with equal or greater facility. Brownell and Sweet (1952, personal communication) have recently tried to make a different use, in a therapeutic sense, of the ability of malignant gliomas to concentrate boron. By exposing the patient to an atomic pile which explodes the intracellular concentrate, disappearance of the tumour is a possibility.

Summary

A method of locating and demarcating brain tumours, using P^{32} and a Geiger–Müller probe counter, is described. It is a valuable additional aid to the surgeon at operation in selected cases, particularly in the taking of a small biopsy specimen through a burr-hole.

We are indebted to Dr. C. S. Gilbert, of the Christie Hospital, Manchester, for his assistance in starting this work and to Dr. Ralston Paterson for providing the isotope.

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DYNAMICS OF HEART FAILURE*

BY

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Professor of Medicine in the University of London, at the Postgraduate Medical School of London, W.12

LECTURE II

Mitral Stenosis

The evolution of mitral stenosis shows a variety of reactions of considerable diversity and interest. The relation of the varied haemodynamic responses to different degrees of valvular obstruction and of associated mitral incompetence is not yet fully understood. A great many facts, however, have been collected, and these can be seen to fall into various patterns (Bayliss *et al.*, 1950a). In discussing pressures in the pulmonary artery in mitral stenosis it should be kept in mind that in normal subjects the lung vessels dilate to accommodate the increased blood flow of moderate exercise without any significant increase in pressure (Hickam and Cargill, 1948).

Some mitral stenoses are so mild as to cause little in the way of radiological signs, and many of these show an absence of any rise in pulmonary vascular pressures, at least at rest. More than half the patients, however, show elevation of pulmonary vascular pressures at rest and in a few pulmonary hypertension is extreme.

There is a well-recognized group of mitral stenotics with some associated mitral incompetence who have massive dilatation of the left auricle. There is little or no detectable enlargement of the pulmonary artery. Daley and Franks (1949) have shown that these patients may be astonishingly comfortable for many years and even for decades. On the radiological evidence of absent pulmonary artery enlargement they surmised that there was little pulmonary hypertension. This surmise seems to be correct. In one example the pulmonary systolic pressure was 36 mm. Hg at rest, and the patient was capable of increasing her cardiac output from 3.8 to 6.2 litres a minute on effort. Although the pulmonary pressure rose *pari passu* (36 to 63 mm. Hg) with the cardiac output, it subsided very rapidly to nearly normal in a minute or two after the exercise was over. This contrasts with the reaction to effort in other mitral stenotics (cf. Fig. 8). The relative mildness of symptoms in this group is presumably related to the absence or transient nature of pulmonary vascular engorgement.

The auricle must hold the blood which flows into it while the ventricle is contracting. Opdyke *et al.* (1948) have shown that the left auricle is normally less distensible than the right. If the auricle is small the normal volume inflow will cause a considerable rise of pressure during the later part of ventricular systole, but if the chamber is greatly enlarged the pressure will not rise nearly so much (Dock, 1949). The same volume of blood can be accommodated in a large chamber with less linear stretching of its walls. It seems possible, therefore, that a very large auricle may permit the maintenance of a reasonable blood flow through the lungs at a lower pressure than would otherwise be required.

In another group of mitral stenotics the pulmonary artery is enlarged radiologically: the pressure in the pulmonary artery is moderately elevated at rest but rises to very high levels during exercise. It is an interesting point that the rise in pulmonary artery pressure which takes place during exercise in mitral stenosis in such patients is not associated with any significant increase in the cardiac output (Fig. 8). During exercise,

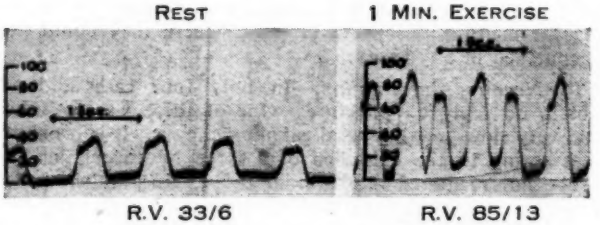

FIG. 8.—A woman aged 37 with mitral stenosis. Exercise increased the pulmonary arterial systolic pressure from 33 to 85 mm. Hg without significant cardiac output change.

therefore, resistance to blood flow through the lungs is considerably increased. The resistance might conceivably develop as a result of shorter diastolic time from the resulting tachycardia. Where diastole is short there is less time for the left auricle to empty into the left ventricle, and blood could collect in the left auricle until pressure was high enough to restore flow through the narrow valve in the limited diastolic time. The second alternative is that a vasoconstrictive reaction develops in the pulmonary arterioles. In favour of the latter hypothesis are the following facts:

(*a*) Acceleration of the heart by atropine in a few instances of mitral stenosis has not in our experience been accompanied by any significant rise in pulmonary arterial pressure (unpublished).

(*b*) Studies with the dye method on pulmonary blood volume show that this is not greater than normal during exercise (Ball *et al.*, 1952). If elevation of pulmonary vascular pressures had resulted from a rise of pressure in the left auricle an increased blood content of the lungs might be expected.

*The second of two Oliver–Sharpey Lectures delivered to the Royal College of Physicians of London on March 11 and 13. The first lecture appeared in last week's issue.

(*c*) During exercise there is an increased pulmonary arteriolar resistance (Draper *et al.*, 1951), and Eliasch *et al.* (1952) have also shown that the pulmonary arterial pressure rises out of proportion to the pulmonary capillary pressure.

Another group of mitral stenotics have gross pulmonary hypertension. The pulmonary artery enlarges and great hypertrophy of the right ventricle becomes obvious on clinical and electrocardiographic examination. Pulmonary artery pressures are found to be elevated to systolic figures between 90 and 150 mm. Hg at rest. With the tachycardia of effort the mean pressure rises to still higher levels, although the systolic pressure may not rise any further. These extreme elevations of pressure, which may on occasion exceed the systemic arterial pressure in the same individual, can reasonably be ascribed only to an increased pulmonary arteriolar resistance. The studies of Dexter and his associates (1950) have shown that when pulmonary capillary pressure rises above 25 mm. Hg in mitral stenosis the pressure in the pulmonary arteries rises to very high levels, and it is clear that a considerable pressure gradient has developed between the main pulmonary artery and the capillaries (Table I*). Therefore the pulmonary arterioles are constricted. It is noteworthy that the pulmonary arterial pressure rises higher in these mitral stenotics than in any of the other common varieties of acquired heart disease (Table I).

These curious vascular reactions in the lung contrast sharply with those usually seen in left ventricular failure. In the latter, failure tends to be episodic, punctuated by dramatic attacks of orthopnoea, recovering with rest and digitalis. In mitral stenosis, by contrast, a chronic obstruction to flow is present at the mitral valve, and perhaps by its very persistence a variety of adaptations result. Enlargement of the left auricle to some extent buffers the effects of congestion and, alternatively, the development of gross pulmonary hypertension throws the load on to the right ventricle, with some resulting protection of the lung capillaries and pulmonary veins, especially during exercise. In the severe pulmonary hypertensive group, where the right ventricle takes the load, effort tolerance may remain remarkably good for some years. One such patient rejected for military service occupied himself as a lumberjack during the war; a second served in the strenuous African campaigns; while a third took part in athletic pursuits, and a few months before the finding of our record pulmonary arterial systolic pressure of 150 mm. Hg was playing club cricket. It is tempting to think that an intermediate stage in the development of persistent severe pulmonary hypertension in mitral stenosis is a phase of pulmonary arteriolar constriction in exercise. Gorlin *et al.* (1951), however, still find this matter debatable.

These unexpected varieties of vascular reaction in the lungs of mitral stenotics are now being supported by other evidence. The dye method of estimation of intrathoracic blood volume has shown no very significant increase in the pulmonary blood volume in mitral stenotics, as contrasted with patients in left ventricular failure, who do show the expected increased pulmonary blood volume (Kopelman and Lee, 1951). Angiography of the lung blood vessels in mitral stenosis has been shown by Goodwin *et al.* (1952) to demonstrate a well-defined narrowing of the pulmonary arteries in the neighbourhood of their tertiary divisions. Other factors involved in the reduction of the lung vascular bed may, of course, be pulmonary emboli, which are so frequent in the later stages of mitral stenosis. The lung arterioles show quite remarkable thickening and may even show necrotizing arteriolitis in mitral stenosis with severe pulmonary hypertension (Larrabee *et al.*, 1949).

In the complex and variable haemodynamic circumstances of mitral stenosis it is not to be wondered at that responses to digitalization are more unreliable than those seen in left ventricular failure. Digitalis only occasionally produces a significant increase in the usually low cardiac output. Similarly, Howarth *et al.* (1947) showed that theophylline ethylenediamine, usually producing striking responses in left ventricular failure, had little effect on mitral stenotics. Digitalis can decrease ventricular tachycardia in auricular fibrillation, but it cannot strengthen a fibrillating auricle or change a sclerotic mitral buttonhole. With a fixed obstruction ahead, increasing the strength of a failing right ventricle may merely increase pulmonary vascular pressure with little clinical benefit. Fig. 9 shows the action of digoxin on a hypodynamic right ventricle in mitral stenosis with a pronounced increase in pulse pressure. The rise in pulmonary pressure is out of proportion to the scarcely significant change in cardiac output, and examples like this cause us to wonder if a full dose of digoxin sometimes increases pulmonary vascular resistance in the same manner as it may increase systemic arterial pressure.

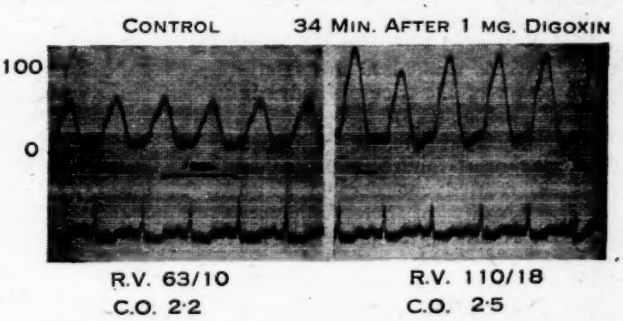

FIG. 9.—Increase in right ventricular pulse pressure in mitral stenosis following digoxin: the cardiac output increase was slight and possibly pulmonary vascular resistance was increased.

The effect of reduction of ventricular rate in auricular fibrillation in mitral stenosis could conceivably give more time for an engorged left auricle to empty through the narrow valve into the ventricle, and one or two instances in which digitalis was accompanied by significant cardiac output improvement had, in fact, been fibrillating with a rapid ventricular response. Kelly and Bayliss (1949), in a general study of the effects of rate reduction by digitalis, showed that reduction of rate played little part in cardiac output improvement, but their study included other varieties of heart failure as well as mitral stenosis, and in some of the latter the ventricular rate was not unduly rapid before digitalization.

Apart from a reduction of tachycardia, then, drug treatment of the chronic failure of mitral stenosis does not offer very much. It is for this reason that surgical help has been welcomed in recent years. Even though gross anatomical changes in the pulmonary arterioles may occur in the severe pulmonary hypertensive group, these are in no sense a bar to operation. Brock (1951) has been able to report that very high pulmonary arterial pressure can fall considerably after successful valvotomy. He gives an example in which pulmonary systolic pressure fell from 130 mm. Hg before operation to 40 mm. Hg after operation.

Tricuspid Insufficiency

When the right ventricle becomes grossly dilated, particularly in mitral stenosis, the tricuspid valve may become incompetent. In some instances it is also shrunken by the direct effect of rheumatic inflammation to the point of virtual disappearance as a functioning valve. Under these circumstances very gross pulsations take place during right ventricular systole in the central caval-auriculo-ventricular

*Table I appeared in the first lecture, which was published in last week's issue.

pool (Fig. 10). The veins beyond the nearest functioning venous valves collectively replace the auricle. Blood is held up in those veins during ventricular systole and then flows on into the central pool in diastole. We thus have the phenomenon of a higher mean pressure in the great veins near the heart than that recorded in the peripheral veins. In cases such as this the liver shares in the pulsation of the central venous pool. On occasion the downhill course of heart failure with pulmonary engorgement seems to be changed for the better by the development of tricuspid incompetence, for it is impossible for the right ventricle to maintain pulmonary engorgement with a large backward leak into the great veins. Adams recognized this safety-valve action of the tricuspid valve in 1828 (Rolleston, 1928).

The subject of Fig. 10, who had developed heart failure in pregnancy in 1939, created considerable alarm by the severity of her pulmonary oedema: following the pregnancy her activity was much restricted. By 1943, however, she had developed gross tricuspid incompetence with a pulsating liver; but there was no peripheral oedema, and the lung fields had cleared radiologically with disappearance of her dyspnoea. She remains remarkably well to-day, is able to do her housework, and has been capable of milder social activities over the last 10 years. The overworking right ventricle is clearly functioning very physiologically and a new equilibrium has been established.

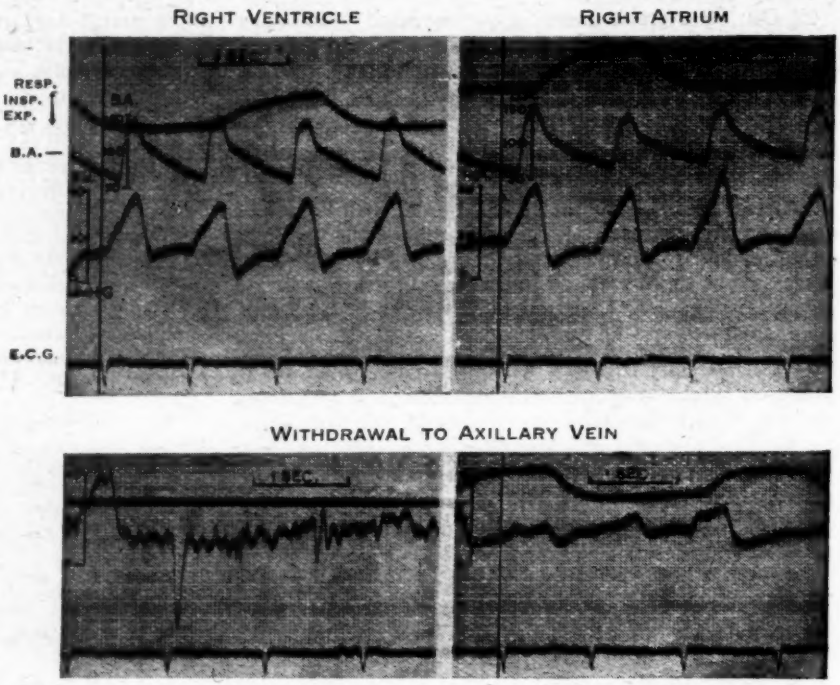

FIG. 10.—Woman aged 37 (R.H.D., M.S., T.I.). Pressures in the right ventricle, right atrium, innominate and axillary veins (lower right) in gross tricuspid incompetence. Note the sudden drop in pressure as soon as the catheter is withdrawn through a nearly competent venous valve. The last record (lower right) shows a slight rise in pressure during ventricular systole, possibly due to a slight leak through the valve.

Cossio and Perianes (1949) have actually recommended the creation of tricuspid valvular incompetence as a treatment for severe mitral stenosis. Unfortunately, such good results from the spontaneous development of tricuspid incompetence are unusual, and when tricuspid insufficiency appears it is more often a manifestation of extreme failure and marks a phase in the downhill progression of the disease.

Pericardial Disease

Disease of the pericardium, whether it consists of an effusion or an adherent rigid case restricting movement, interferes with filling of the heart. Dr. Charles Fletcher (1945) published a study on a single case showing that the rise in venous pressure in pericardial effusion was simply enough to maintain a more or less normal effective filling pressure of the heart in excess of the external pressure upon it. When fluid was removed from the pericardium, filling pressure and external pressure upon the heart fell in parallel and the output remained unchanged. We have since repeated this observation in a pericardial effusion resulting from Hodgkin's disease with essentially similar results.

In constrictive pericarditis the tracings of right ventricular pressure are very characteristic (Fig. 11). During early diastole there is a steep dip in pressure followed by a quick rise to a diastolic plateau at a high pressure level (Eliasch *et al.*, 1950). As blood rushes in from the auricle, limited expansibility of the ventricle causes the pressure to rise rather steeply to a plateau, at which it is maintained until the ventricle contracts. In contrast with most other types of heart failure the right ventricular pulse pressure remains normal. Pressure in the veins near the heart is high, corresponding to the high diastolic filling pressure of the ventricle. Digitalis is without influence on the pressure curves, cardiac output, or venous filling pressure in such cases.

The protodiastolic sound of constrictive pericarditis coincides with the steep dip in ventricular pressure (McKusick, 1952). The careful studies of Hansen *et al.*

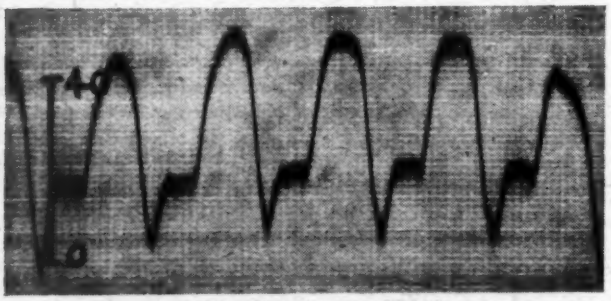

FIG. 11

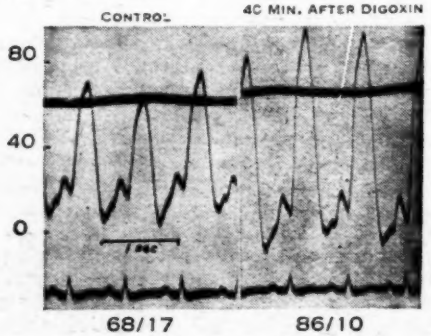

FIG. 12

FIG. 11.—Right ventricular pressure curve in a male with constrictive pericarditis. Note the steep dip of pressure in early diastole and the sharp rise to a plateau. The pulse pressure (43—19) is normal. FIG. 12.—Rheumatic aortic incompetence in severe failure. The right ventricular pressure in diastole rises steeply, somewhat like constrictive pericarditis. The pulse pressure is high and rises still higher under digitalis.

(1951) show that this early diastolic dip is not an artifact as might be suspected (Katz, 1930). Fibroplastic endocarditis and myocardial fibrosis may produce similar curves (McKusick, 1952; Hansen *et al.*, 1951). It is to be noted that a similar dip and rapid climb to a higher level may be seen in some cases of severe heart failure. The shape of the curve in the latter cases may alter with digitalization, the pressure dip becoming less obvious as the diastolic filling pressure of the ventricle comes down to a lower level (Fig. 12).

Acute Nephritis

In acute nephritis a state of affairs may be seen which is barely distinguishable from hypertensive heart failure (Davies, 1951). The blood pressure is raised moderately, the venous pressure is nearly always high in the acute phase (La Due, 1944), and, of course, there is a well-recognized liability to the development of more gross cardiac failure, the incidence of which has been put at figures ranging from 20% (Ellis, 1936) to 71% (Whitehill *et al.*, 1939), depending on the severity of congestive phenomena demanded by the authors as their criteria. In the cases we have studied, which have shown only raised venous pressure, the cardiac output has been normal and there has been no response of either cardiac output or venous pressure to digitalization. It would therefore seem that these cases were not in a hypodynamic state.

It is at present difficult or impossible to put one's finger on the initiating mechanism of this type of heart failure. It may be hypertensive, or it may be that retention of salt and water creates haemodilution and a circulatory overload. A somewhat similar state of affairs can be induced in normal subjects by the administration of D.C.A. and salt.

The Present Position

In our earlier studies we were limited to right auricular filling pressure and cardiac output changes in the consideration of types of heart failure. Our approach to-day tends to put much less stress on cardiac output change, for heart failure may be present at any level of resting cardiac output, and considerable clinical improvement can take place without any change in cardiac output so long as elevated pressure, particularly in the lungs, is relieved. The function of a single ventricle may be assessed not only on the amount of blood which it ejects but also on the magnitude of the pulse pressure it can achieve at any given diastolic tension.

In the whole complex pattern of heart failure we should recognize *hypodynamic congestion* likely to be relieved by digitalis so long as the terminal unresponsive stage has not been reached, and *compensatory states of congestion* in which the drug seems to have little effect (Table II).

TABLE II.—*Causes of Heart Failure*

Cause of Load	Myocardial Function	
1. Valvular: obstructive and backflow lesions	Compensatory, or "physiological"	High venous pressure
2. Myogenic: damage or destruction of muscle by inflammation, oxygen lack, or ischaemia		
3. Mechanical: pericardial disease		
4. Extrinsic:		
Physical: systemic hypertension; pulmonary hypertension; anaemia; Paget's disease; salt and water retention; nephritis; D.C.A.; etc.	OR	
Metabolic: beriberi; hyperthyroidism; uraemia; cholaemia	Hypodynamic, or "pathological"	

In the production of venous congestion there are many factors. The mechanical effect of valvular obstruction and of tricuspid incompetence may create a true backward pressure. In still other instances, where there is no valvular obstacle and where the resting output is actually high, there is clearly no obstruction to flow within the heart, and the high pressure in the veins must result from an increased volume of blood within them or an increased tone of the venous wall.

Some recent observations by Braun and Fryd (1951) and Halmágyi *et al.* (1952) have shown that the administration of sympathicolytic and ganglionic blocking agents lowers the venous pressure in most forms of heart failure, and that such venous pressure reduction is absent in normal subjects. These effects indicate the possible importance of autonomic control of venomotor tone, a possibility I have previously stressed (McMichael, 1949). There are, however, several other consequences of the administration of such drugs, and the subject clearly requires more detailed analysis.

There are various peripheral vascular reactions in heart failure which must also be taken into account. In the high-output types with a normal arterial pressure (anaemia) there must be peripheral vasodilatation. Conversely, the low-output types are associated with vasoconstriction and cold extremities. Brigden and Sharpey-Schafer (1950) have shown that patients with left ventricular failure develop reflex peripheral vasoconstriction in recumbency as contrasted with vasodilatation which takes place in normal subjects. Recumbency may precipitate attacks of orthopnoea, and in acute attacks of left ventricular failure the systemic arterial pressure is practically always found to be elevated above the previous level. The place and nature of these reactions in the complex picture of acute left ventricular failure still remain to be clarified. We can all observe from time to time in the dying patient with left ventricular failure an intense peripheral constriction which may lead to actual gangrene of the tip of the nose and fingers (Swan and Henderson, 1951). In one such patient Dr. Graham Bull (unpublished) demonstrated that there was also a very gross reduction of renal blood flow to less than one-tenth the normal value.

Past Errors and Future Prospects

It is now some 16 years since I became involved in the study of haemodynamics in heart failure. I have been intrigued and fascinated by the digitalis problem and have constantly sought some explanation of its striking success in some cases and equally miserable failure in others. The possible clue of primary venous pressure reduction influencing the healthy and failing heart in different ways was thoroughly explored some eight years ago. Though superficially attractive the idea was abandoned as soon as inconsistencies came to light. There are other explanations for failure of digitalization, partial successes, and complete success, as I hope I have shown. We have had to learn in a painful and difficult transition that the unitary conception of heart failure as a single entity was incorrect. A large number of variables are involved in the complex interaction of the two sides of the heart, each of which may be in a different dynamic state when failure is developing. Congestive phenomena can certainly make their appearance in the absence of a hypodynamic myocardium. The responses of the lung vessels, as seen in mitral stenosis, may produce a further series of complex reactions altering the picture. Pure pulmonary heart failure in emphysema seems to result from episodes of pulmonary hypertension occurring in the bronchitic attacks (Mounsey *et al.*, 1952).

Knowing my own fallibility only too well, I wish to emphasize that I have merely presented a current view of heart failure. Researches with modern tools began only some five years ago. The sequence of events between the beginning of heart disease and the development of congestive phenomena is still a matter of speculation. Starr (1949) produced experimental infarction of practically the whole of the right ventricle of a dog with no resulting measurable rise in venous pressure. Conversely, I hope it has become clear that some patients with venous engorgement have normally functioning, though loaded, right hearts. So what do we mean by right heart failure? The term is too loosely used. When patients with myocardial infarction develop congestive phenomena a few days have usually elapsed from the acute episode, and in a few more days the congestion may vanish. What is happening during this sequence

of events? Why does the cardiac patient pass into a dying state with a resting minute volume of circulation the same as that of an upright soldier?

The realization of ignorance brings its gleam of hope that continued research will add to our therapeutic power: cardiac surgery and new technical developments in investigation are adding daily to our knowledge and extending our experience in depth. In time some of the pictures crudely sketched in these lectures will be more clearly perceived, and be submitted once again to a much more rational and complete interpretation than we can give to-day.

(Figs. 5, 6, and 7 are reproduced from *Acta Medica Scandinavica*, 1952, Supplement 266, p. 701, by kind permission of the Editor.)

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Whales are popular among doctors nowadays. Not only are their pituitary glands a useful source of A.C.T.H., the whales are also the quarry of the cardiologist. Dr. Paul D. White has recently returned to Boston from Alaska with a one-ton beluga whale's E.C.G. The electrodes were brass-headed harpoons (*Time*, August 25).

RHEUMATIC FEVER

SOME OBSERVATIONS ON A.C.T.H., CORTISONE, AND SALICYLATE THERAPY

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Hench and his colleagues (1950) have demonstrated the rapid benefit afforded by A.C.T.H. and cortisone to sufferers from rheumatic fever. They could not, however, determine whether such treatment lessened the incidence or degree of valvular damage. They also showed that these hormones have a profound effect on the metabolism of protein, fat, carbohydrate, and electrolytes, and that the continued administration of them led to some of the clinical and biochemical changes observed in Cushing's syndrome. Treatment with salicylate has hitherto been the basic method and evidence is accumulating that this well-tried remedy actually engenders adrenocortical excess. In this paper we give an account of the use of A.C.T.H. and cortisone in four selected cases of rheumatic fever and describe the response of four other cases to treatment with salicylates. We add to the evidence that salicylate has an A.C.T.H.-like effect, and we give our present impressions of the value of A.C.T.H., cortisone, and salicylate in the treatment of rheumatic fever.

Cortisone Treatment

We gave the cortisone to severely ill patients who had not responded to salicylates. The dosage in each case is set out in Fig. 1. Cortisone acetate was given by intramuscular injection daily for six days each week. We thought at first that the hormone could be discontinued once we had abolished the tachycardia, corrected the anaemia, and reduced the raised E.S.R. to normal. As will be seen, recrudescence of the disease often followed the cessation of treatment at such a stage. Because of this and the similar experience of others (Dorfman *et al.*, 1951) we increased the period of therapy by at least four to six weeks, with the aim of suppressing these signs. The duration of treatment varied from 44 to 110 days.

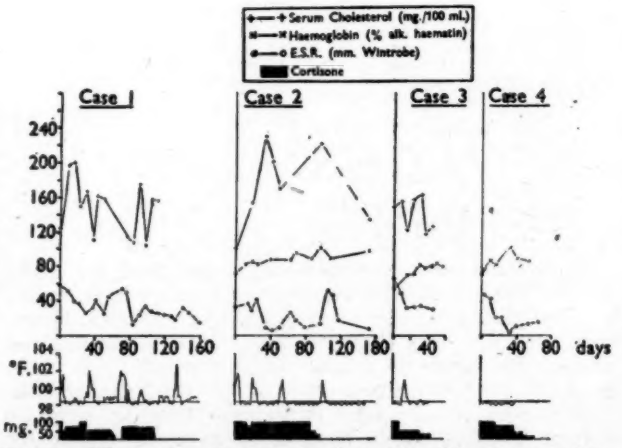

FIG. 1.—Effects of cortisone on patients who did not respond to salicylates.

Case 1

The patient, a boy aged 9, had no previous history of rheumatic disease. Two weeks before admission he developed a sore throat and then arthritis. When admitted on October 12, 1950, he was pyrexial, with a tachycardia, and a systolic murmur was heard at the mitral area. With salicylate therapy the pulse rate and temperature fell to normal by the fifth day, and by November 29 the E.S.R. was 16 mm. (Westergren). He was discharged on December 20, only to be readmitted five days later with a relapse. Pyrexia and tachycardia persisted despite penicillin and salicylate therapy. Because of tinnitus the dose of salicylate was reduced, and three days later he was worse and there were signs of pericarditis. On January 23, 1951, a typical erythema marginatum appeared. The lower lobe of the left lung was compressed, the liver was enlarged, and the feet and scrotum were oedematous. Haemoglobin was 66% and the E.S.R. 58 mm.

Cortisone treatment was begun on January 24. The next day the rash was fading and no friction rub was heard. He was apyrexial one week later, when the displacement of the apex beat was less and tachycardia had decreased. During the second week, with mercurial diuretics, the liver was less enlarged and the oedema cleared. After four weeks' treatment the dose was reduced to 50 mg. daily. A short bout of fever followed at once. During the following weeks it was evident that the disease was not controlled. When cortisone was discontinued in the ninth week, high fever, tachycardia, and joint pains returned. They were soon relieved by 75 mg. of cortisone daily. Reduction of dosage in the fourteenth week was followed by transient fever. When treatment was discontinued after four months moderate fever returned. He was given aspirin, and after his transfer to Queen Mary's Hospital, Carshalton, the fever subsided and he felt well. On discharge from that hospital there were no signs of carditis.

Case 2

A boy aged 15 was admitted on March 5, 1951. He was known to have heart disease due to rheumatic fever and chorea. Four days before admission he developed joint pains, sweating, and fever. On admission he had a sore throat and the left wrist and right knee were inflamed. His heart rate was 110, and blood pressure 160/20. The heart was enlarged to the mid-axillary line, and signs of mitral stenosis and aortic incompetence were present. Haemoglobin was 73%, and the E.S.R. 54 mm. He was given acetylsalicylic acid, 8 g. daily. By the seventh day he was apyrexial and his pulse rate was 80. On March 15 he developed fever due to an alveolar abscess; penicillin was given and the tooth extracted. Blood cultures were negative. Pyrexia continued, and a few days later he had pains in his knees and ankles. Pericardial effusion was suspected. Haemoglobin was 67%, and the E.S.R. 60 mm.

On April 13 penicillin and salicylates were discontinued and cortisone therapy was begun. Two days later his general condition was worse. He was drowsy, his joints were still painful, and his temperature did not subside until April 19. Blood cultures taken meantime were negative. By April 23 he was much improved. When the cortisone dosage was reduced to 75 mg. daily, rheumatic nodules appeared; pyrexia, tachycardia, and joint pains persisted for five days after the dosage was restored. In the seventh week another attempt at reduction of dosage was followed by a rise of temperature. Cortisone was finally discontinued after 14 weeks, and was withheld even though he became pyrexial and the E.S.R. had increased. We hoped that this was a manifestation of temporary adrenocortical insufficiency (see below). His nodules had slowly decreased in size and were not visible by this time. A few days later the fever settled, although the E.S.R. did not become normal for three weeks. There were no symptoms during this period. He subsequently remained well, and he thought that his dyspnoea was no worse as a result of this attack of rheumatic fever.

Case 3

A boy aged 9, with established rheumatic heart disease following rheumatic fever and chorea, was admitted on January 25, 1951, with severe epistaxis; signs of mitral stenosis and aortic incompetence were also present. Epistaxis recurred, and the haemoglobin fell to 46%. He was transfused on February 3 and immediately became febrile. On February 6 he had joint pains, dyspnoea, and tachycardia. There were scattered petechiae, and a pericardial friction rub was audible. Blood cultures were negative. On February 7 calcium aspirin was administered. On the following day the patient had no pain, he was pyrexial, and the rub was no longer audible. On February 16 the temperature rose again, he was dyspnoeic, and the heart was further enlarged. On February 21 a pericardial rub was again audible, the haemoglobin had fallen to 54% and the E.S.R. was 55 mm.; treatment with cortisone was begun. Two days later he was brighter and less dyspnoeic. The friction rub was not audible after February 26. Oedema then developed, but he was still on a high dosage of aspirin. This was discontinued, mercurials were given, and the oedema subsided. Transient pyrexia followed reduction of cortisone dosage. He maintained his recovery when cortisone was discontinued after 44 days.

Case 4

A girl aged 14, with no previous history of rheumatism, was admitted to another hospital on April 21, 1951. Three weeks before admission she had a sore throat followed by arthritis and fever. On admission her heart was enlarged to the anterior axillary line, and a systolic murmur was audible at the mitral area. Haemoglobin was 70% and the E.S.R. 126 mm. (Westergren). Joint pains subsided on 150 gr. (10 g.) of sodium salicylate daily, but fever persisted. On April 28 the serum salicylate was only 15 mg. per 100 ml. and dosage was increased to 180 gr. (12 g.) daily. On May 4 the serum level was 38 mg. per 100 ml. and the dosage was halved for a few days. On May 7 widespread nodules appeared and the temperature rose; a week later a pericardial rub was heard.

On May 21 she was transferred to this hospital. Her general condition was worse. Nodules lay as rows of beads over the extensor tendons of the fingers and toes, over the wrists and ankles, on the ulnar borders of the forearms, over the elbows and knees, scapulae, and occiput. Cortisone treatment was begun immediately. Two days later she was much improved. The friction rub was not heard after four days, she was apyrexial, and the heart was smaller. The rheumatic nodules rapidly decreased in size, and after two weeks' treatment could not definitely be discerned, except over the left elbow, where they persisted until July 18. The haemoglobin and E.S.R. had become normal one month before, at which time the systolic murmur was not audible. She had cortisone for 58 days and

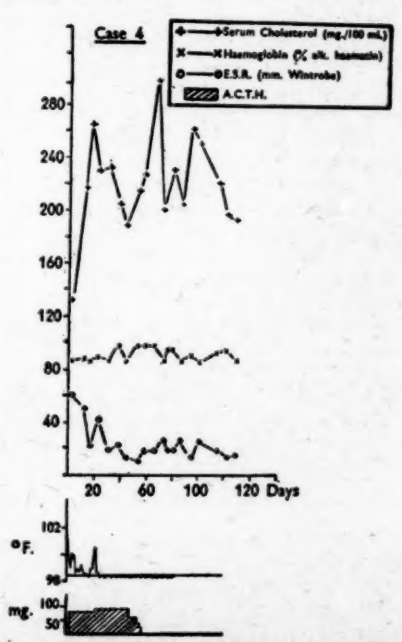

FIG. 2.—Showing response to A.C.T.H. in Case 4.

was transferred to a convalescent home. She later relapsed there, and was readmitted to this hospital and given A.C.T.H. (see below).

A.C.T.H. Treatment

Case 4 was transferred to a convalescent home on July 29, 1951, 12 days after cortisone was discontinued. She there gained weight rapidly. During August haemolytic streptococci were cultured from the throat and she was given penicillin on September 6. Her temperature rose and a loud systolic murmur was heard. The E.S.R. was 100 mm. On September 8 she was brought back to this hospital and treatment was promptly begun. A.C.T.H., 10 mg., was given by intravenous drip overnight, and then 20 mg. every six hours intramuscularly. After two days she was apyrexial and the heart rate was normal (Fig. 2). The systolic murmur remained rough and she had occasional joint pains. After 20 days the A.C.T.H. was increased to 15 mg. every four hours. From then on there was progressive improvement and the murmur softened. After 28 days A.C.T.H. was discontinued. She was gradually got up and remained well. A soft systolic murmur has persisted. There is no sign of cardiac enlargement on radioscopy.

Salicylate Treatment

With the hormone-treated cases above we found that the serum total cholesterol rose to a high level. We therefore decided to find if a similar increase occurred with salicylate treatment. We selected patients with first attacks of rheumatic fever. Fig. 3 gives the results of laboratory investigations and the dosage of acetylsalicylic acid. The drug was given as "berex" tablets. Each tablet contains acetylsalicylic acid, 3.7 gr. (250 mg.), and calcium succinate, 2.8 gr. (190 mg.). Dosage was designed to keep the level of salicylate in the serum above 30 mg. per 100 ml. (as salicylic acid by the Tarnoky method (Tarnoky *et al.*, 1950)). This high dosage was well tolerated.

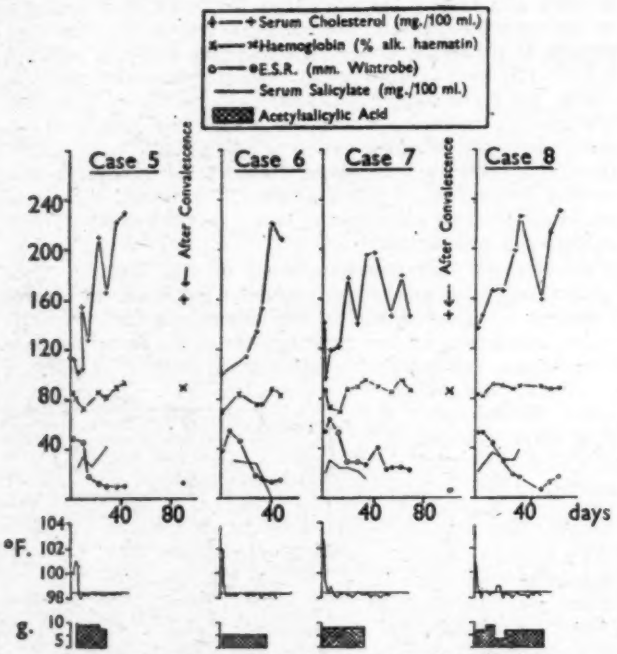

FIG. 3.—Showing results of treatment with salicylates.

Case Summaries

Case 5.—A girl aged 8 was admitted on October 9, 1951, and discharged on November 22. She had tonsillitis eight days before admission, and four days later her legs became painful. On admission there was erythema over both knees, which were inflamed. She was pyrexial, her heart rate was 120, and the heart sounds were soft. During the first four days her temperature and pulse rate were raised, but the joint inflammation subsided. She was then treated with berex tablets. The temperature became normal overnight, while the pulse rate returned to normal after seven days. No cardiac murmurs were heard at any time. Her antistreptolysin (A.S.O.) titre reached 3,000 units on November 1.

Case 6.—A girl aged 5 was admitted on September 21, 1951, and discharged on November 13. Five days before admission she developed pain in her knees. When she was admitted these joints were warm and tender, her temperature was 102.8° F. (39.3° C.), and the pulse rate was 134. A soft systolic murmur was audible at the apex. Treatment was begun the next day. She quickly improved, and the pulse rate was normal by the end of the first week. The soft systolic murmur was not heard after the third week. The A.S.O. titre reached 840 units on October 3.

Case 7.—A girl aged 17 was admitted on November 7, 1951, and discharged on January 24, 1952. Before admission she had a sore throat, followed a week later by pain in the lower limbs. She was admitted the next day with a temperature of 103° F. (39.4° C.). There was widespread joint inflammation, with erythema over the ankles; the heart sounds were softened. Treatment was started the same day. After four days the joints were normal. On the fifth day she was apyrexial. During the second week a soft systolic murmur was audible at the apex, but this diminished and was not audible on discharge. Cardioscopy then showed the heart to be normal in size. The A.S.O. titre was 400 units on November 12.

Case 8.—A girl aged 14 was admitted on November 12, 1951, and discharged on March 13, 1952. Early in October she had a sore throat, followed a week later by pain in the right knee. This responded to salicylates at home, but when the dose was reduced the knee again became painful and pyrexia recurred. On admission the temperature was 101° F. (38.3° C.), and pulse rate 130. The right knee and ankle were inflamed; the heart appeared normal. Treatment was begun the next day. After two days she was apyrexial, and after four days there was no tachycardia. Pain in the left elbow recurred on November 21, but subsided when the dosage was increased. After reduction of the dosage on November 29 the temperature rose and joint pain recurred. Dosage was again increased and she became well. The A.S.O. was 400 units on November 26.

Laboratory Investigations

During treatment weekly estimations of haemoglobin (alkaline haematin method), white blood count, E.S.R. uncorrected (Wintrobe), and serum sodium, potassium, chloride, and total cholesterol were made. Consistent changes were observed only in the haemoglobin, E.S.R., and serum total cholesterol. These results are shown in Figs. 1 and 2. The haemoglobin rose steadily until discharge, when the levels were all above 80%. In all cases E.S.R. readings fell with the initial therapy, only to rise again on reduction or termination of treatment. At discharge all readings were normal or nearly so. The serum cholesterol showed a steady rise during the first month with cortisone, A.C.T.H., and salicylate treatment. With cortisone, reduction of dosage was promptly followed by a fall in the serum cholesterol. In two of the salicylate-treated cases (Cases 5 and 7) cholesterol estimations were done daily for the first few days, and an initial fall of serum cholesterol was observed in both. These investigations were made because A.C.T.H. is reported to differ in its action from cortisone in that there is a fall of the serum cholesterol during the first days of administration (Conn *et al.*, 1950).

Side-effects

Cortisone Treatment.—Special care was taken to look for any of the side-effects that have been reported to follow hormone therapy (Hench *et al.*, 1950). No patient showed any mental disturbance during treatment. The initial torpor

was soon replaced by normal mental vigour. The appetite was increased—enormously in Case 2. Purple striae developed on the back in Case 2 and on the buttocks in Case 4. Slight acne was seen in Cases 1 and 2. Rounding of the face appeared in all cases by the end of the first month. It became very marked in Case 2, in which neck and trunk thickened with obesity. Case 1 also showed deposition of fat on the trunk after two months. Oedema was present in Case 1 at the start of treatment. Case 3 developed oedema after five days' treatment; by an oversight he was still taking a large dose of aspirin. Mercurial diuretics soon cleared the oedema.

A.C.T.H. Treatment.—Case 4, who had gained weight while away at the convalescent home, developed a rounded face and a dorsal pad of fat during A.C.T.H. treatment. Thin red radiating striae developed on both breasts, similar to those observed during pregnancy. The patient, although 14 years old, had not yet menstruated.

Salicylate Treatment.—All patients showed rounding of the face and an increased appetite. Case 7 developed red radiating striae on both breasts similar to those observed in Case 4.

Discussion

Response to Hormone Therapy.—The presence or absence of a past history of rheumatic disease seems to have had no bearing on the response to treatment. Within a few days the patients became symptom-free and apyrexial. Signs of cardiac inflammation disappeared; the pulse rate fell to normal, the heart size diminished, and in the two cases with a first attack the systolic murmur disappeared. If we accept the old teaching that nodules are evidence of active endocarditis, then their rapid dissolution in Case 4 may have been parallel to a resolution of the endocarditis. After reduction of dosage or termination of treatment there usually was a return of fever, and often of joint pain; one patient (Case 2) even developed nodules. Sprague *et al.* (1950) attribute this flare-up to adrenocortical insufficiency induced in the patient by the exogenous cortisone. When cortisone is administered to experimental animals the adrenal cortex decreases in size, and after the cortisone is discontinued several days must pass before the cortex is restored (Winter *et al.*, 1950). Once the adrenal cortex is restored the flare subsides if the rheumatic activity that is present is slight enough to be suppressed by endogenous adrenal activity. Wilson and Helper (1951) have seen similar flares following A.C.T.H. treatment, and thought them to be due to an inhibition of the anterior pituitary. Case 1 showed a true and continued relapse when cortisone was discontinued. Here the disease may not have reached its natural termination, or a throat infection present at that time may have been responsible.

A.C.T.H. was given to only one patient—Case 4 of the cortisone series, when she had a recurrence due to a throat infection. Improvement followed at once, but the dosage was increased from 20 mg. every six hours to 15 mg. every four hours before satisfactory control was obtained. We did feel that the A.C.T.H. had averted a serious recurrence, but the persistence of a systolic murmur seemed to indicate that valvular damage had occurred.

Side-effects.—We saw very few of the side-effects found by other workers, and none was of serious consequence. The striae do persist after their colour has faded. We could not weigh our patients while they were confined to bed, but weight gain was apparent in all and continued after the treatment ceased. All our patients were young and growing, and some gain in weight was to be expected, but the obesity of two of them lingered.

Adverse Effects.—The most serious early adverse effect that has been reported is an increase of heart failure in the days following the beginning of treatment (Carlisle, 1950; McEwen *et al.*, 1950). This increase is due to the retention of sodium and water, and usually abates when a diuresis occurs on continued treatment or a mercurial diuretic is given. The low-salt diet may have protected our patients. Cortisone and A.C.T.H. mask the presence of infection, and it is likely that a throat infection might go unnoticed by the patient. This is an added reason for precautions against cross-infection in the ward. The prophylactic administration of penicillin is recommended by some. A throat swab should certainly be taken every week.

Corticogenic Hypothyroidism.—Fig. 1 demonstrates the rise of the serum cholesterol that occurred in our cases treated with cortisone, and Fig. 2 the rise with A.C.T.H. therapy. This response to these hormones has been noted by Adlersberg *et al.* (1950) and by Conn *et al.* (1950). Wolfson *et al.* (1951) believe that this rise is due to the development of hypothyroidism. They have demonstrated that A.C.T.H. and cortisone lower the plasma-bound iodine level and decrease the radioactive iodine uptake of the thyroid, and they call this "corticogenic hypothyroidism."*

Effect of Salicylates

We sought for and found changes in the serum cholesterol level when cases of rheumatic fever were treated with salicylates (Fig. 3). The response of serum cholesterol to A.C.T.H. differs from that of cortisone in that there is a fall during the first days of administration (Conn *et al.*, 1950).

In two of the salicylate-treated cases daily readings were begun, and these showed an initial fall of serum cholesterol—that is, resembling the response to A.C.T.H. This finding is in line with the view of Hetzel and Hine (1951), based on other evidence, that salicylate leads to an increase of A.C.T.H. production. We admit that salicylate may have an antithyroid effect by combining directly with available iodine, but we have been unable to do this *in vitro* as Bull and Fraser (1950) were able to do for resorcinol, and the initial fall of serum cholesterol favours the first explanation.

A more elaborate investigation is clearly necessary to determine whether the rise of serum cholesterol with salicylate therapy is due to hypothyroidism and whether it is mediated via the pituitary–adrenal axis. Salicylate and cortisone both have an antipyretic effect and reduce the E.S.R. They both cause retention of sodium chloride and water, and then diuresis (Reid *et al.*, 1950). They both increase uric acid excretion and cause loss of potassium and nitrogen. There is decreased glucose tolerance (Cochran *et al.*, 1950) and hyaluronidase is inhibited by both (Dorfman *et al.*, 1947). Increased excretion of reducing steroids in response to salicylates has been demonstrated (Van Cauwenberge and Heusghem, 1951). Sayers (1950) suggested that salicylates exert their effect by promoting the utilization of adrenocortical hormones peripherally in the tissues, and that this leads to increased production of A.C.T.H. The pituitary does seem to be necessary, for Hetzel and Hine (1951) were unable to demonstrate either eosinopenia or depletion of ascorbic acid and cholesterol in the adrenals of hypophysectomized rats that were given salicylate, but obtained these responses in normal rats. Meade and Smith (1951) suggest only two points of difference in action between the hormones and salicylate: one is the effect on glycosuria in diabetic rats, and the other is the effect on the clotting-time. A temporary eosinopenia with A.C.T.H. and cortisone is now well known and occurs when salicylate is given (Roskam *et al.*, 1951).

Reid (1948) stressed the electrolyte changes that occur with salicylate treatment of rheumatic fever, and pointed out the danger of the increased plasma volume that is seen in the first few days of administration. We now know that this also occurs with hormone treatment. Cochran *et al.* (1950) observed an increase in body hair, abnormal

*The suggestion that corticogenic hypothyroidism is due to the inhibition of thyroid-stimulating hormone (T.S.H.) is contraindicated by the finding of Perry (1951). He showed in rats that after seven days' cortisone administration there was no change in the thyroid weight. Also, thyroxine, which depresses T.S.H. secretion, lowered the rate of I^{131} *release* from the thyroid, whereas high levels of cortical hormones had no such effect.

fat distribution, and a tendency to acne with salicylate treatment. We have seen red striae developing on the breasts of two girls, one receiving A.C.T.H. and the other receiving salicylate.

Role of A.C.T.H., Cortisone, and Salicylates

We all recognize that it is the carditis that needs to be eliminated if treatment is to be regarded as successful. May Wilson believes that patients who are given A.C.T.H. during the first days of illness are cured of their rheumatic fever (Wilson and Helper, 1951). She stated at the Second A.C.T.H. Conference that A.C.T.H. given "during the acute exudative inflammatory phase before there is irreversible damage results in termination of the acute rheumatic process" (*Proceedings of A.C.T.H. Conference*, p. 627). Other speakers at the conference stated that A.C.T.H. was not curative in their early cases. They pointed out that patients seen shortly after the illness began usually responded well to salicylate treatment, and implied that this was evidence against Dr. Wilson. All speakers were in agreement that cases of long duration showed only a suppression of the rheumatic process in response to treatment with cortisone and A.C.T.H.

Coburn (1943) believes that high and prolonged salicylate dosage is essential for the removal of clinical evidence of carditis and leads to a greatly reduced incidence of subsequent valvular disease. Satisfactory serum salicylate levels are often not maintained, however, because dosage is reduced on account of tinnitus or other toxic effect. The level fluctuates widely even on the same dosage, and it is not generally known that sodium bicarbonate, often prescribed with sodium salicylate, lowers the serum level (Smith *et al.*, 1946). We would stress, too, that the sodium salt should be avoided. For these reasons, and because of the natural severity of the disease in some patients, many cases of rheumatic fever are not relieved by salicylate therapy.

We have, to date, no conclusive evidence that hormone therapy is better than salicylates in reducing cardiac inflammation, but A.C.T.H. and cortisone do in fact suppress fever and nodules where salicylates have failed.

We started with 100 mg. of cortisone intramuscularly daily when treating children and adults. If given orally the dose should be increased by a fifth to obtain the same degree of response. Better initial suppression would be achieved by larger initial doses, and we should now give 300 mg. for a few days and then continue with 125 mg. as maintenance dosage. Severely ill patients should be watched for the increased plasma volume in the first days of treatment. The customary dose of A.C.T.H. is 25 mg. intramuscularly every six hours. If this is insufficient, 20 mg. every four hours will exert more effect than 30 mg. every six hours. Salicylate should be given in full dosage and should maintain a serum level above 30 mg. per 100 ml. The sodium salt is best avoided. As with hormone therapy, the diet should contain little sodium.

Conclusion

We believe it reasonable to hold as a working hypothesis that the chief pharmacological activity of salicylates is in some way related to the metabolism of corticosteroids. Similar clinical and biochemical changes occur with the administration of salicylates, cortisone, and A.C.T.H. The aim when any of these substances is used in the treatment of rheumatic fever should be to achieve a rapid resolution of symptoms, a normal cardiac rate, a fall of the E.S.R. to normal, and a steady rise of haemoglobin. These changes will depend mostly on a satisfactory dosage. These features should be present for at least four to six weeks before treatment is discontinued. Relapse will then occur only if the rheumatic state should still exist in the patient; but false relapse due to temporary pituitary or adrenal insufficiency must be recognized as such when hormone dosage is reduced, and will then last no more than a few days. A.C.T.H. and cortisone seem to be more certain in action than salicylates; that they are also more potent is suggested by the greater ability to induce Cushing-like effects. We believe that A.C.T.H. and cortisone will prove to be the best forms of treatment for most cases of rheumatic fever. Salicylates should be adequate as routine treatment, especially in early cases, and this is important while the cost of the hormones remains high. We do not yet know to what extent the morbid anatomical changes of rheumatic disease are reversed by treatment, and comparison between hormones and salicylate is difficult. Whether or not the incidence or severity of valvular disease is curtailed has yet to be determined.

Summary

Four children severely ill with rheumatic fever and pericarditis showed a prompt improvement when treated with cortisone. The duration of treatment varied from 44 to 120 days. With reduction of dosage the signs and symptoms of rheumatic activity recurred. There was no increase of disability in the two patients who had previous rheumatic valvular disease. In the other two patients it was their first attack. One was left without apparent heart damage; the other appeared to be fully recovered, but shortly after relapsed following a throat infection. This patient responded to a course of A.C.T.H., but a systolic murmur persists.

In all of these cases some clinical features of adrenocortical excess were observed. Weekly examination of the serum cholesterol showed a constant rise during administration of either hormone. Four patients were then treated with high dosage of salicylates, and clinical and biochemical changes, similar to those in the hormone-treated cases, were noted. In particular, mention must be made of the development of red striae on the breasts of two girls, one treated with A.C.T.H. and the other with salicylates. The administration of salicylate was found to lead to an initial fall of the serum cholesterol followed by a rise which was maintained throughout the treatment. This initial fall resembles that seen when A.C.T.H. is given.

It was concluded that it was justifiable to hold as a working hypothesis that salicylates exert their pharmacological activity by engendering adrenocortical excess. When salicylate, A.C.T.H., and cortisone are administered, rheumatic activity is suppressed. The criteria of dosage and of duration of treatment are the same when any of these substances is used.

ADDENDUM

We have observed the serum cholesterol in two further cases of acute rheumatism treated with salicylates. The cholesterol figures, on the days of treatment shown, conform to the pattern described above.

	Serum Cholesterol (mg. per 100 ml.)													
Day:	1	2	3	4	5	6	7	14	21	28	35	42	49	56
Case 9	168	120	130	156	195	—	188	230	192	230	—	—	235	270
,, 10	108	87	88	87	128	136	—	190	122	—	194	170	158	188

We wish to thank Dr. E. T. Conybeare, of the Ministry of Health, and Dr. James Graham, of the North-east Metropolitan Regional Hospital Board, for the supply of A.C.T.H. and cortisone. The Berex Pharmaceutical Company kindly supplied us with berex tablets. We wish to thank Dr. F. H. Bryning, medical superintendent, and Dr. J. A. Cardno, consultant physician, at Hackney Hospital, for their co-operation in this work, and Dr. K. J. Samson, of the German Hospital, who asked us to give cortisone to one of his patients. We are indebted to Dr. E. Hardy, of the Group Laboratory, Mile End Hospital, for his unstinted help in the laboratory investigations.

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RELATION OF ELECTROLYTE CHANGES AND ADRENOCORTICAL ACTIVITY TO PARALYTIC ILEUS

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There has been much speculation about the cause of paralytic ileus ever since Thomas Sydenham (1666) differentiated the condition which he referred to as "true ileus" from the "bastard ileus" caused by mechanical obstruction. Sydenham thought that "true ileus" was due to fever which brought about a "commotion of the blood" so that "acrid and malignant humours are lodged in the stomach and in those parts of the intestinal canal that lie nearest to it." Other "commotions of the blood" have continued to enjoy recognition as possible causes of the condition now known as paralytic ileus, and in recent years the suggestion has been made that electrolyte deficiencies may be among the responsible agents.

It has been known for some time that hypertonic sodium chloride infusions stimulate vigorous peristalsis in experimental animals (Hotz, 1909) and in patients with paralytic ileus (Hughson and Scarff, 1924). More recently, French authors (Robineau, 1933; Lévy and Nora, 1935, 1946) have attributed paralytic ileus to the low concentration of chloride observed in the plasma and in the blood cells in this condition, and have attempted to prevent the onset of ileus by the routine administration of large amounts (45–50 g.) of sodium chloride daily in the immediate post-operative period. Marriott (1947) has also suggested that chloride deficiency may be the cause of some cases of ileus, and Streeten (1950) has shown that the propulsive motility of actively contracting preparations of human intestine can be abolished by their immersion in fluid with a lowered chloride concentration similar to that which occurs in the plasma of patients with paralytic ileus.

Maddock (1939) found that post-operative hypochloraemia refractory to isotonic sodium chloride administration abated when the patients began to eat a normal diet. This observation prompted Ariel, Abels, Pack, and Rhoads (1943) to administer large amounts of protein orally and parenterally to patients with post-operative ileus associated with the same sodium-chloride-refractory hypochloraemia; their five patients all responded favourably. Randall, Habif, Lockwood, and Werner (1949) suggested that potassium deficiency was responsible for the syndrome described by Ariel *et al.* (1943), and hastened recovery by giving potassium solutions intravenously. Darrow (1950), too, stated that intestinal distension and paralytic ileus are among the results of potassium deficiency.

The clinical suggestion that potassium deficiency may cause paralytic ileus is considerably strengthened by a rapidly accumulating body of experimental evidence. Winter, Hoff, and Dso (1949) showed that the tone and motility of the whole gastro-intestinal tract were reduced, and the passage of a barium meal retarded, in rats made deficient of potassium either by repeated injections of deoxycortone or by lowering potassium intake. Webster, Henrikson, and Currie (1950) reported similar results in rats, but found that in dogs with potassium deficiency there was only a slight reduction in the strength and rate of rhythmical contractions of the alimentary tract. Streeten and Vaughan Williams (1952) have found that fluid transport by intestinal loops can be abolished in dogs by progressive sodium chloride depletion. The intestinal paralysis came on only when, as a result of chloride deficiency and adrenocortical stimulation, a rapid loss of cellular potassium took place, causing a sudden increase in the plasma concentration of this ion. When the propulsive motility of intestinal segments was abolished *in vitro* by reducing the sodium chloride content of the surrounding fluid, it was possible to demonstrate a large fall in the potassium concentration of the bowel wall and a consequent rise in the concentration of this ion in the surrounding fluid. In other unpublished experiments it was not possible to paralyse dog intestine by reducing the potassium concentration of the external medium to as low as 5 mg./100 ml. for periods of over an hour.

The recent evidence is therefore consistent with the view that intracellular, though not extracellular, potassium deficiency can cause paralysis of gastro-intestinal motility both *in vivo* and *in vitro*. The present study was undertaken in an attempt to discover the relation of potassium and chloride deficiency and adrenal cortical hyperactivity to the development of paralytic ileus in man.

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Clinical Material and Methods

Thirteen patients with paralytic ileus were studied in Oxford, 11 during 1950 and 2 at the beginning of 1951 (Table I). Eosinophil and leucocyte counts were made

TABLE I.—*Particulars of 13 Patients with Paralytic Ileus*

Case No.	Sex	Age	Diagnosis and Operation	End of Ileus (Post-op Day)	Outcome
1	M	61	Acute obstruction due to carcinoma of pelvic colon: laparotomy and caecostomy	7th	Died 12th post-op. day
2	M	68	Perforation of sigmoid colon: laparotomy and colostomy	8th	Recovery
3	M	66	Carcinoma of rectum: synchronous combined abdomino-perineal excision	6th	Died 9th post-op. day
4	M	48	Carcinoma of stomach: total gastrectomy, splenectomy, hemipancreatectomy	5th	Recovery
5	M	57	Perforated gastric ulcer with generalized peritonitis: operative repair	8th	,,
6	M	44	Jejunal ulcer: high partial gastrectomy	6th	,,
7	F	65	Carcinoma of head of pancreas: cholecyst-jejunostomy, jejuno-jejunostomy	5th	Recovery; died a month later
8	F	61	Appendicitis with general peritonitis: appendicectomy	8th	Recovery
9	M	21	Appendicitis: appendicectomy. General peritonitis; pelvic abscess	10th	,,
10	M	37	Acute pancreatitis: laparotomy. Burst abdomen 10th post-op. day	7th	,,
11	F	49	Ruptured tubo-ovarian abscess: salpingo-oophorectomy	7th	,,
12	M	44	Duodeno-jejunal obstruction due to metastases of carcinoma of kidney: gastro-enterostomy. Burst abdomen 9th post-op. day	8th	Recovery; died 11 days later from sudden haemorrhage
13	F	43	Mesenteric thrombosis: resection 6 feet of ileum	6th	Recovery

by Randolph's (1944) method, and packed cell volumes with matched Wintrobe tubes spun at 3,000 r.p.m. for 30 minutes. Trichloracetic acid extracts of blood cells were prepared for estimations of mean erythrocyte potassium concentration (M.E.K.C.) with a flame photometer, which was also used for estimations of potassium and sodium in plasma and in 24-hour collections of urine, gastro-intestinal aspirations, and H_2SO_4-extracts of faeces (Peters and Van Slyke, 1932). Chloride concentrations in plasma, whole blood, urine, aspirations, and faecal extracts were estimated by Van Slyke and Hiller's (1947) modification of the micro-method of Sendroy (1937). Mean corpuscular chloride concentrations (M.C.Cl.C.) were calculated from the formula

$$\text{M.C.Cl.C.} = \frac{\text{whole blood Cl} - \left(\text{plasma Cl} \times \frac{100 - \text{haematocrit}}{100}\right)}{\text{haematocrit}} \times 100$$

For this estimation the haematocrit was read to the top of the buffy coat (layer of leucocytes), since preliminary studies showed that leucocytes and erythrocytes had approximately similar chloride concentrations. After recovery, patients were given a diet of known electrolyte content.

Repeated references will be made in this paper to unpublished results of blood chemical and balance studies made on a series of seven patients for four to six days before and six to ten days after a variety of elective major surgical procedures comparable to the operations which had preceded the onset of ileus in the present series of patients.

Onset and End of Ileus.—The onset and end of paralytic ileus cannot be defined accurately. In these patients the diagnosis rested on the absence of bowel sounds on repeated examination, failure to pass flatus or faeces, and vomiting or the aspiration of large volumes of fluid by an indwelling naso-gastric tube, associated with abdominal distension, after the third post-operative day. The ileus was thought to be over when the bowels were opened or flatus was passed repeatedly, although the distension often persisted.

Management of Cases

All the patients received penicillin, and all but one had soluble sulphadimidine injections. Streptomycin was also given to eight patients who were thought to have peritonitis. Injections of morphine were given occasionally to most of the patients, but more frequently to only three of them. Amidone replaced morphine in some of the later patients. Naso-gastric suction by Ryle's tube was used in 11 patients, and in only two was a Miller-Abbott tube passed. Most of the patients were allowed 1 oz. (30 ml.) of fluid by mouth hourly, and were given combinations of water, Ringer's solution, 5% dextrose, fruit juice, citrated milk, and 1% potassium chloride in orange juice. Three blood transfusions (1 or 2 pints—570 or 1,140 ml.—each) were given to six patients, three of whom also received plasma infusions. The first six patients received saline, dextrose, and Ringer's solution intravenously, while the other group of seven patients was given in addition infusions of Darrow's solution (NaCl 6 g., KCl 2.7 g./litre) in an attempt to correct the deficiency and replace the daily losses of potassium. Two of the first group of patients, Cases 1 and 3, died six and three days respectively after having repeated bowel movements. All seven patients in the second group recovered, one (Case 7) dying a month later from generalized carcinomatosis, and another (Case 12) dying from sudden gastro-intestinal haemorrhage 11 days after recovery from ileus, while he was up and about taking a normal diet.

Changes in the Eosinophil and Leucocyte Counts

When the patients were first seen the eosinophil count was below 60 per c.mm. in 9 of 11 cases examined. Serial eosinophil counts were made in seven patients who survived (Fig. 1) and two who died. The count remained low for as long as the ileus continued, but rose abruptly on the day

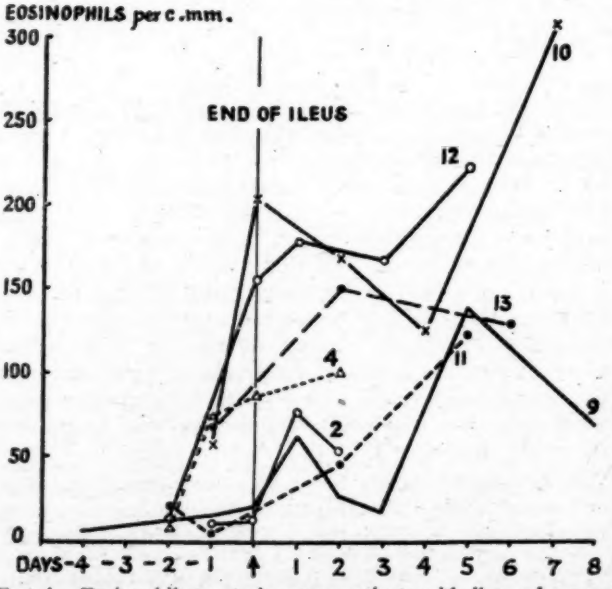

FIG. 1.—Eosinophil counts in seven patients with ileus who survived. The vertical line indicates the end of ileus, and the ciphers are the patients' serial numbers (see Table I).

the ileus was considered to have ended, or immediately before or after this day. Thereafter the count fluctuated within normal limits. The two fatal cases had normal eosinophil counts when they were first seen four and five days after operation. After a few days both patients passed large amounts of intestinal contents through a caecostomy and colostomy respectively, and this continued, while the leucocyte and eosinophil counts fell progressively, until the patients died.

A leucocyte count of less than 4,000 per c.mm. was observed at some stage of the ileus in 6 of the 13 cases, including two of the five patients with very severe drum-like distension. Most of the leucocyte counts were within normal limits (4,000–10,000 c.mm.), however, in spite of the fact that many of the patients had severe infections. These findings confirm the report of Van Duyn (1942) that leucopenia often occurs in patients with severe abdominal distension.

Blood Electrolyte Changes

Potassium.—The plasma potassium concentration varied widely in the 10 patients in whom repeated estimations were made, and no consistent changes were observed. Low values varying from 9.4 to 15.2 mg./100 ml. were recorded in five patients when first seen. At the time of recovery two of these patients showed a rise which continued, but four still had low values (10.3 to 14.5 mg./100 ml.) several days later. The M.E.K.C. in most of the cases of ileus was not below the levels (359–418 mg./100 ml., mean 382.2, S.D. 23.5) observed on the fourth post-operative day in normal convalescence. At the time of recovery from ileus, however, five out of six patients showed an increase, but one a progressive fall in M.E.K.C. (Fig. 2). In two of three other patients in whom only single estimations were made, low values (311 mg./100 ml. and 314 mg./100 ml.) were found several days after recovery. No consistent changes could be found in the ratio between the erythrocyte and plasma potassium concentrations.

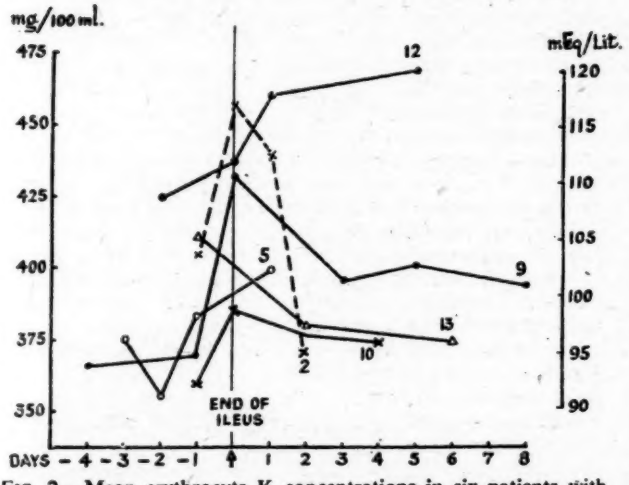

FIG. 2.—Mean erythrocyte K concentrations in six patients with paralytic ileus. The vertical line indicates the end of ileus

Chloride.—The plasma concentration of chloride was below 560 mg./100 ml. (as NaCl) in all of the patients when first seen in ileus (Table II). In 9 of the 13 patients there was a gradual rise in plasma chloride concentration from when they were first seen, followed by a more rapid rise to normal levels (550–630 mg./100 ml.) on the day of recovery, or immediately before or after that day. In two other cases the values remained low for several days after the recovery of bowel function. In patients on whom elective surgical operations were performed the mean of the estimations of M.C.Cl.C. has been found to be 318 mg./100 ml. (S.D. 22.6) before the operations and 313 mg./100 ml. (S.D. 21.9) on the fourth post-operative day; all the estimations done four days after operation fell between 280 and 333 mg./100 ml. Seven out of 10 of the present series of patients had an M.C.Cl.C. below 280 mg./100 ml., and one patient had a low normal value at 286 mg./100 ml. Normal levels were reached in all patients after recovery from ileus, though this usually took a few days. In three of the patients there was a greater reduction in mean corpuscular than in plasma concentration. This was reflected in a cell/plasma ratio which was below the normal range (0.47 to 0.59, mean 0.54, S.D. 0.037) found in surgical patients before operation. Normal cell/plasma chloride ratios were reached on recovery in these patients.

Sodium.—The plasma sodium concentration was reduced below 315 mg./100 ml. in 5 of the 10 patients in whom it was estimated in ileus. In only one of these patients did the concentration rise above 315 mg./100 ml. on the day of recovery or during the succeeding two days, normal levels being reached in the remainder from three to five days after bowel movements had returned.

Changes in the Electrocardiogram

Electrocardiograms were obtained on five patients during ileus, and each showed evidence of potassium deficiency, with depression of the ST segment and prolongation of the Q–T interval.

Since the Q–T interval varies with the heart rate, the observed duration of the Q–T interval was compared in each patient with the normal duration, calculated from the formula (Bazett, 1918–20) $Q\text{–}T = K \times \sqrt{\frac{60}{\text{heart rate,}}}$ where K = 0.40 for women and 0.37 for men. The observed Q–T intervals were in all cases longer than the normals calculated from the formula; after recovery from ileus there was a tendency to return towards the normal Q–T duration in the two patients examined.

TABLE II.—*Results of Plasma Chloride Estimations in 13 Patients with Paralytic Ileus (Values in mg./100 ml., as NaCl)*

Case No.	Days Before Recovery					Day of Recovery	Days After Recovery								
		−4	−3	−2	−1		+1	+2	+3	+4	+5	+6	+7	+8	
1				495	527	559	564	538	529	572	703	Death			
2		525			562	574	567	562							
3				533	504	506	590	707	699	Death					
4				505	540		595		580				575		
5		522	534	526	523		554	558			549				
6			551			550			549	568					
7		445	406		506	480			497	477				518	615
8		496									579				
9		534			540	548	585	574	565		564			523	
10					524	565		574		529			568		
11	545		522				542					554			
12		454		484		479	493		526		579				
13			559		530	550		580				600			11th 665
Mean ..	508·0				528·4	534·6	561·3	584·7	563·6	572·8					

Gastro-intestinal Aspirations

Large amounts of sodium, chloride, and potassium were lost in the aspirated gastro-intestinal contents (Table III). The concentrations of the electrolytes varied somewhat among the patients in the series, but were surprisingly constant from day to day in any one of the five patients who received Ringer's solution, citrated milk, or water in hourly volumes of 1 oz. (30 ml.) by mouth. Three of the patients were given concentrated potassium chloride solutions by mouth during ileus, but it was found that a variable proportion, frequently almost all, of the ingested potassium was recovered in the gastric aspirations, indicating that little reliance could be placed on absorption of potassium administered by this route in paralytic ileus.

TABLE III.—*Electrolytes in Gastro-Intestinal Aspirations*

	Mean	Range
Na	200 mg./100 ml.	150–343 mg./100 ml.
Cl (as Cl)	303 mg./100 ml.	178–426 mg./100 ml.
K	37 mg./100 ml.	22–89 mg./100 ml.

A striking change was observed in the colour of the 24-hour specimens of aspirated material. When the patients were first seen the aspirations were dark green and contained much biliverdin, but little or no bilirubin. A day or two before the end of ileus the aspirated material became yellow or reddish, and always contained bilirubin (positive van den Bergh reaction) but no biliverdin.

Urine and Faeces

The urine passed during the 24 hours after the patients were first seen with ileus was always small in volume; it contained very low concentrations of sodium and chloride and a high concentration of potassium. After treatment for a variable number of days there was a sudden reduction in the urinary potassium and an increase in urinary sodium and chloride excretion, all of which occurred on the day of recovery from ileus, or one to two days before or after this day. The increase in sodium excretion preceded that of chloride in most patients. The reduced potassium and increased sodium and chloride output at the time of recovery occurred in spite of the fact that the intake of these ions was kept fairly constant or was changed in the directions opposite to the urinary changes. Fig. 3 shows that these urinary changes occurred at about the same time as the rise to normal levels of the eosinophil count in the seven patients (Cases 7 to 13) in whom both estimations were made.

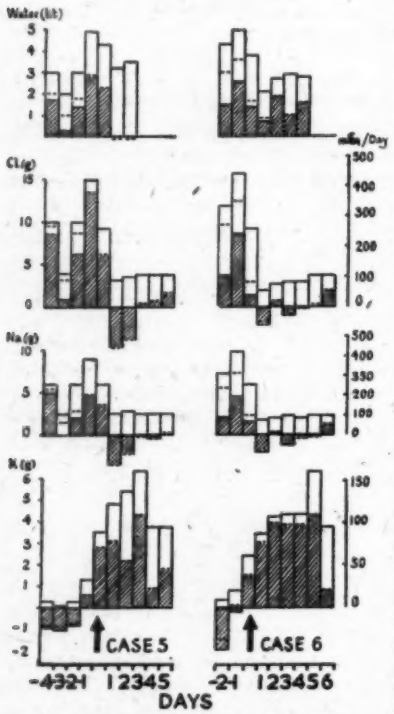

FIG. 3.—Water, Cl, Na, and K balances in Cases 5 and 6. Daily intake is charted from the base-line upwards, and daily output from the top of each intake column downwards. Urinary output is unshaded and separated from aspirations by a dotted line; balances are cross-hatched. Balances above the base-lines are therefore positive. No allowance has been made for insensible water loss. The end of ileus is indicated by the arrows.

The sodium, chloride, and potassium content of the faeces was estimated in five patients (Cases 8, 9, 10, 12, and 13). Some of the patients in the series passed repeated large diarrhoeal stools and suffered from incontinence on their recovery from ileus, and a complete collection of faeces was impossible. In any one of the patients the faecal electrolyte concentrations were fairly constant, daily variations from the mean being seldom more than 30%. The variation between patients was very large indeed, sodium concentration varying between 41 and 630, chloride (as Cl ion) between 52 and 231, and potassium between 66 and 542 mg./100 ml.

Balances

The water, chloride, sodium, and potassium balances in Cases 5 and 6 are shown in Fig. 3. As in Cases 7 to 13 (see Fig. 4), there was a sudden reduction in the large urinary output of potassium at about the time of recovery from ileus. A marked diuresis of sodium, chloride, and water took place at the time of recovery in both patients. It is evident that these changes in electrolyte excretion were in the opposite direction to the variations in their intake and could not be attributed to this cause. Both patients retained large amounts of water, sodium, and chloride during ileus, but were restored to normal balance within two to three days of the return of bowel function. Delay in the excretion of administered sodium chloride may have been partly responsible for the sudden diuresis of sodium and chloride at the time of recovery. However, excretion of a sodium chloride load in normal individuals is seldom as long delayed as in these patients, in whom the occurrence of a sudden rise in the eosinophil count at the same time provided additional evidence of a hormonal mechanism inducing the changes in urinary electrolyte excretions.

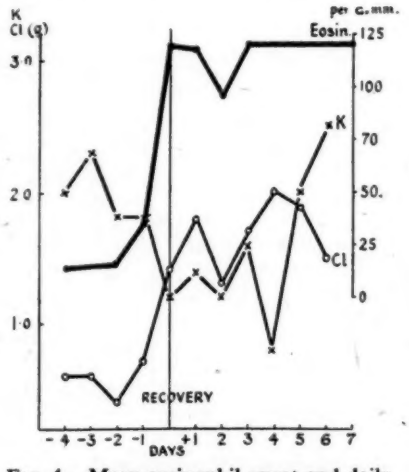

FIG. 4.—Mean eosinophil count and daily urinary output of K and Cl in seven patients (Cases 7 to 13). The end of ileus is indicated by a vertical line.

The balances in the patients in whom faecal losses were estimated indicated that the apparent positive balances of sodium and chloride during ileus and of potassium after recovery cannot be explained as being due to the loss of these electrolytes into the bowel lumen. The negative potassium balance present in ileus was replaced after recovery by a period of great potassium retention; the mean daily retention of potassium, in patients in whom faecal losses were estimated, was 2.5 g. for the first two to four days after recovery.

Discussion

Adrenocortical Activity in Ileus

An eosinopenia was observed in 9 of 11 patients with paralytic ileus. At this time, more than three days after operation, the eosinophil count would be expected to be within normal limits if recovery was uncomplicated (Roche, Thorn, and Hills, 1950; Coppinger and Goldner, 1950; Johnson, Conn, Iob, and Coller, 1950). On the other hand, in patients who develop infection or other post-operative complications causing prolongation of the usual adreno-

cortical response to the operation, eosinopenia will persist, often in the absence of leucocytosis, as long as the complication is present, in the same way as eosinopenia will be observed for the full duration of continuous intravenous A.C.T.H. infusions lasting as long as 10 days (Thorn, 1952). The persistent eosinopenia in paralytic ileus even in the presence of normal or lowered leucocyte counts probably, therefore, indicates an unusual prolongation of the normal post-operative increase in the secretion of 11-oxysteroids by the adrenal cortex. It is well known that these steroids promote an increase in the urinary excretion of potassium, and all of our patients were found to have a high output of potassium in at least the first of the 24-hour specimens of urine analysed four or more days after operation. Wilkinson, Billing, Nagy, and Stewart (1950b) and our own unpublished results have shown that at this stage in a normal convalescence the urinary potassium output has fallen after its initial post-operative increase. The presence of persistent adrenocortical hyperactivity in ileus is further indicated by the sudden reduction in urinary potassium output and the diuresis of water, sodium, and chloride which occurred at the end of ileus.

Potassium Deficiency

After a prolonged urinary excretion of potassium and in the absence of its replacement, these patients with ileus would be expected to be severely deficient in potassium. The loss of large amounts of gastro-intestinal contents still further aggravated this depletion. It is difficult to demonstrate cellular deficiency of potassium which may be associated with a normal or raised plasma potassium concentration. If the loss of potassium from the cells continues for long enough, urinary excretion of the ion will eventually result in a lowered plasma potassium level, as was found in 5 out of 10 of our patients. A deficiency of cellular potassium is strongly suggested by the findings in the five patients on whom electrocardiograms were done. The results of the M.E.K.C. estimations failed to provide further definite evidence of cellular potassium deficiency. However, there was a sharp rise in M.E.K.C. at the time of recovery from ileus in five of the six patients in whom repeated estimations were made. This rise occurred at about the same time as the increase in the eosinophil count and was reminiscent of a similar rise in M.E.K.C. which coincided with the end of the eosinopenia between two and three days after uncomplicated operations. Strong evidence of potassium deficiency during ileus was obtained from the balance studies, which demonstrated that large quantities of potassium were retained after recovery in all cases.

Chloride Changes

The changes in chloride were probably of less consequence. All the patients had a lowered plasma chloride concentration, usually associated with a relatively slight reduction in plasma sodium. The lowered plasma chloride concentration cannot, however, be attributed to urinary excretion of chloride, since there is retention of both chloride and sodium with the loss of only very small quantities of both these ions in the urine for periods of four to eight days after major operations. Furthermore, our patients with ileus all had very low urinary chloride concentrations when first seen. The reduced plasma chloride is possibly secondary to loss into the alimentary tract, or it may be the unexplained accompaniment of cellular potassium deficiency, to which Darrow (1948) and others have drawn attention. The reduced erythrocyte chloride concentration in ileus was also found by the French workers Robineau (1933) and Lévy and Nora (1933), but it is impossible to say whether this reduction is attributable to potassium depletion, or how far chloride deficiency *per se* contributes to the paralysis of the bowel in ileus.

Pathogenesis of Ileus

In patients with paralytic ileus there is good evidence both of prolonged adrenocortical hyperactivity and of the potassium deficiency which this is known to produce. Experimental work has shown that deficiency of intracellular potassium results in a condition in animals indistinguishable from paralytic ileus in man. It seems reasonable, therefore, to suggest that the gastro-intestinal features of ileus may be due to potassium depletion, which, in turn, may result from prolonged adrenocortical hyperactivity and reduced intake of potassium. Three objections to this hypothesis immediately come to mind.

First, cortisone and A.C.T.H. have often been given in high doses without potassium salts, and, while alkalosis with low plasma chloride and potassium concentrations has resulted, there have been no reports of ileus. It is possible that the loss of potassium is more severe or more rapidly produced in patients developing ileus than in those receiving hormonal treatment; for Winter *et al.* (1949) have shown that deoxycortone, which is more potent in its potassium-diuretic effects than is cortisone, impairs the gastro-intestinal motility of rats. This possibility is strengthened by the fact that patients on cortisone or A.C.T.H. therapy are usually eating a normal diet, with a fairly high potassium content, whereas in patients developing ileus there has almost always been a period of at least three days after operation during which virtually no potassium has been taken. Evidence from three of our patients suggests that paralytic ileus is caused not by adrenocortical hyperactivity *per se* but by the potassium deficiency which it induces. In Case 9 paralytic ileus ended when the potassium deficiency had been overcome, but the eosinopenia persisted because of adrenocortical activity induced by a large pelvic abscess. On the other hand, the two fatal cases had normal eosinophil counts when first seen. Both patients were, however, severely depleted of potassium because of the unreplaced losses of this ion during the immediate post-operative period.

A second objection, which is more difficult to reconcile with the hypothesis advanced, is that many patients will recover from paralytic ileus without receiving potassium salts and without complete recovery from electrocardiographic and other signs of potassium deficiency. It may be that the abrupt termination of adrenocortical hyperactivity found at the end of ileus causes a redistribution of body potassium, resulting in a replenishment, from skeletal muscle stores, of the potassium contained not only in the erythrocytes, as has been shown, but also in the intestinal muscle.

Thirdly, while the increased adrenocortical activity during ileus and its abrupt termination at the end of ileus suggests an intimate relationship between adrenocortical hyperfunction and paralytic ileus, it may be argued that ileus is the cause, and not the result, of the increased adrenocortical secretion. This possibility cannot be eliminated, but seems unlikely. Most types of "stress" will certainly stimulate an increase in the output of steroids by the adrenal cortex. It is possible that intestinal paralysis *per se* may have the same effect, but there is no direct evidence that it does.

In conclusion, there would seem to be more reason to believe that infection (which was present in eight cases in this series), or some other agent, is responsible for the excessive adrenocortical activity which, through potassium deficiency, may be a factor in causing ileus.

Intravenous Therapy in Paralytic Ileus

A full discussion of the treatment of ileus is beyond the scope of this paper. Whether deficiency of potassium is or is not the cause of post-operative paralytic ileus, patients with this condition are almost always deficient in potassium, and will sometimes die unless this deficiency is corrected. If the depletion of potassium, and the losses of sodium and chloride in the aspirations can be corrected, and complications treated, most patients will survive until increased adrenocortical activity subsides and ileus ends.

Intravenous therapy aimed at replacing daily losses and rectifying existing deficiencies is governed by the normal rules (Darrow and Pratt, 1950). The Fantus test (1936) is a convenient means of estimating losses of chloride in the aspirated gastro-intestinal fluids, though its use as an indication of chloride deficiency in the urine is fallacious in the

presence of adrenocortical hyperactivity. If facilities for determining daily potassium losses are not available, the figures obtained in this study afford a rough guide to the patients' requirements. Thus, 1.5–3 g. of potassium was lost each day in the urine, about 0.4 g. of potassium per litre in the aspirations, and an unknown amount into the distended bowel, the fluid faeces after recovery containing 0.5 to 5 g. of potassium per litre. It is convenient to replace the losses of sodium, chloride, and potassium in the aspirations by administering 250 ml. of Darrow's solution (NaCl 6 g. and KCl 2.7 g. per litre) for each litre aspirated. More concentrated potassium chloride solutions, containing no sodium, such as that of Davidsen and Kjerulf-Jensen (1951) (KCl 3.8 g. and dextrose 34 g. per litre), are indicated for the correction of the initial potassium deficiency, but the solutions must be given slowly and only in the presence of adequate urine output, sodium chloride or dextrose solutions being given first, if necessary.

Ramasarma (1951) states that clinical benefits result from the administration of amino-acid solutions to surgical patients, but Wilkinson *et al.* (1950a) consider that intravenous protein is not retained in the post-operative "katabolic" phase.

Suction and the Relief of Distension

In most of our patients symptomatic relief was obtained by Ryle's tube, but patients with severe distension can be afforded greater relief by long intestinal tubes (Miller and Abbott, 1934; Cantor, 1946; Harris, 1945). The importance of distension as the major factor in paralysing the bowel has probably been over-estimated, as eight of our patients remained distended for some days after the return of intestinal movements. In any event, intestinal tubes afford great symptomatic relief and probably reduce the incidence of chest complications, and organic obstruction due to kinking of the bowel.

A large oral intake of fluid before normal intestinal motility is restored appears to encourage paralysis (Begg, 1943).

Stimulation of the Bowel

Attempts to stimulate intestinal motility by such drugs as posterior pituitary extract, neostigmine, and di*iso*propyl fluorophosphate are of little value, certainly until electrolyte deficiencies have been corrected (Streeten, 1950), and may even be harmful (Devine, 1946).

Sedation

Patients with ileus are often justifiably worried and usually badly in need of sleep. Morphine has been shown to cause tonic contraction of the intestine and abolition of propulsive movements for long periods in dogs: it therefore cannot be said to "rest" the bowel. It may be beneficial to begin treatment with a single injection of morphine which may reduce distension, but repeated injections would seem likely to prevent the return of normal intestinal propulsion. Amidone in therapeutic doses has, however, little effect on motility (Vaughan Williams and Streeten, 1950, 1951). Our impression from a clinical trial in which morphine and amidone (10 mg.) were given to 30 alternate patients after similar major operations was that the analgesic effects of the drugs were similar, while the patients who received the amidone were more co-operative and suffered less from nausea.

Summary

Thirteen patients with paralytic ileus were studied in an attempt to discover the relation of adrenocortical hyperactivity and of potassium and chloride deficiency to the development of this condition.

There was evidence of adrenocortical hyperactivity during ileus, with abnormal prolongation of the post-operative eosinopenia, excessive potassium loss in the urine, and retention of water, sodium, and chloride. On recovery the eosinophil count rose, and there was a diuresis of water, sodium, and chloride and a retention of potassium.

Evidence of potassium deficiency rested on excessive loss during ileus and retention after recovery: it was confirmed by electrocardiographic changes. In five out of ten patients the plasma potassium was low and, although the mean erythrocyte potassium concentration was not below normal levels in ileus, there was a definite increase in five out of six patients on recovery.

Low plasma and blood-cell chloride concentrations were found in nearly all patients with ileus. Normal values were regained at about the time of recovery.

There is strong experimental evidence that potassium deficiency produces a state akin to ileus in rats and dogs. The hypothesis that the gastro-intestinal features of paralytic ileus in man are due to potassium depletion as the result of adrenocortical hyperactivity is considered, and the difficulties in accepting this view are discussed.

The importance of replacing lost electrolytes, particularly potassium, in ileus, is emphasized. Amidone is probably superior to morphine as an analgesic in ileus. Most patients recover provided their electrolyte balance is restored and the complications are dealt with.

We are indebted to Mr. D. A. Abernethy for allowing us to treat eight of these patients, and to other surgeons of the Radcliffe Infirmary for allowing us to investigate, and in some cases to treat, the remainder. Our thanks are due to Dr. L. Leyton, of the Department of Forestry, University of Oxford, for the use of his flame photometer; to Miss McLarty for the diagrams; to the dietitians, Miss Hemmin and Mrs. Westland; and to the ward sisters, particularly Sister Whitcombe.

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SINGLE MASSIVE DOSE OF VITAMIN B_{12} IN UNTREATED PERNICIOUS ANAEMIA

BY

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The efficacy of parenterally administered vitamin B_{12} in microgramme doses has been unequivocally shown by Ungley in pernicious anaemia (1949a) and subacute combined degeneration (1949b), and the response of the former to varying doses quantitatively assessed (1949a). Adequate initial and maintenance dosage has been determined for both of these conditions (Ungley, 1950, 1951). The object of this study was to determine whether, in untreated pernicious anaemia, a single dose of vitamin B_{12} greatly in excess of that found to give the optimal initial response would result in a prolonged remission and thereby furnish presumptive evidence of the effective storage of vitamin B_{12} in the body following injection.

In carrying out this object a point of great interest was the duration of the normoblastic response in the marrow following a 1-mg. dose, and the comparison of this with the duration of normal findings in the peripheral blood and the clinical state of the patient. Certain difficulties exist from relatively unknown factors such as spontaneous remissions, but in spite of this the findings in blood and marrow are of much interest, and may throw some light on the question of whether in the treatment of pernicious anaemia larger injections at longer intervals than hitherto are feasible.

Methods

The series comprised 15 patients who were each given a single intramuscular injection of 1 mg. of crystalline vitamin B_{12}. The clinical and haematological findings in each patient fulfilled the accepted criteria for the diagnosis of pernicious anaemia, the most important being macrocytic anaemia, megaloblastic marrow, histamine-fast achlorhydria, normal barium-meal examination, and at least three consecutive negative tests for blood in the stools. When the anaemia was not severe the patients were observed without treatment for periods varying from two to six weeks to exclude a spontaneous remission.

Following the injection, favourable reticulocyte and red-cell responses were obtained in every case, and after discharge from hospital the patients were kept under regular review for clinical and blood examination, as nearly as possible at intervals of one month from the date of injection. On the whole, attendance at the appropriate intervals was good, although there were occasional gaps in the records. The patients themselves and their family doctors were requested to avoid any anti-anaemia treatment other than that given at the follow-up clinic, and we are satisfied that no other treatment was given. No special diet was prescribed after discharge from hospital, and the only additional treatment given was oral iron in full doses to those patients who showed evidence of iron deficiency at any stage. The criteria for relapse in the peripheral blood were a fall in the red-cell count, generally below 4.5 millions, and/or a large or persistent rise in the mean corpuscular volume. Examinations were repeated as necessary when there was reasonable doubt about the significance of the findings. Symptoms such as sore tongue and paraesthesiae would have been taken as indications of relapse, but in fact did not occur when the blood was normal except in one patient just before relapse became evident in the blood.

A further marrow examination was done at least once in each patient, and the time of these marrow studies ranged, in different cases, from 69 to 358 days after the single injection of vitamin B_{12}. Differential counts (400 cells) of the red-cell precursors in these marrows (see Table I) were done, using the classification and nomenclature given by Whitby and Britton (1950), and the appearance of the cells placed in each category follows in general their description, except that the cells classified as late normoblasts had nuclei that were pyknotic or very nearly so. The group of intermediate normoblasts, therefore, is the most heterogeneous one as regards varying degrees of maturation in the cells included in it, and corresponds to the early and late polychromatic normoblasts described by Dacie and White (1949). Like these authors, we have found that this is generally the predominating red-cell precursor in normal marrows.

In the follow-up marrows of this series, with their frequently minor variations from normality, considerable difficulty was sometimes experienced in differentiating promegaloblasts from pronormoblasts as described by Dacie and White (1949). Because the early megaloblast is easily recognized, and as distinction at an earlier phase was not important for our purpose, it was not given a place in the differential counts (see Table I). One type of cell, however, that we, like others such as Mollin and Dacie (1950), have found of great value in detecting slight or partial tendencies to megaloblastic haemopoiesis is the transitional

TABLE I.—*Differential Counts, 400 Cells, of the Red-cell Precursors in 18 Marrow Examinations Done on 14 Patients at Different Time Intervals Following a Single Injection of 1 mg. Vitamin B_{12}. The Time Elapsing Until Detection of Relapse in the Peripheral Blood is Also Given. Where the Space is Blank the Patient is Still in Remission.*

Patient:	1*	2	2	3	3*	4	5	5	5*	6	7	8	9	10	12	13	14	15
Initial R.B.C. (millions per c.mm.)	3·35	1·05		1·9	3·3	0·79	2·1	2·1	3·13	1·64	0·8	1·28	1·9	1·51	1·07	0·8	1·28	2·3
No. of days to marrow examination	93	116	358	107	192	76	69	137	98	110	115	95	150	81	86	95	92	82
No. of days to relapse in peripheral blood	348			150	192	128	132	132	142	182	170	181		81				
Proerythroblasts (%)	2	2	2·5	0·5	4·25	1	2	5	4	4·25	2·5	1·5	0·5	2	2·25	3·25	1·5	1·25
Early (basophil) normoblasts (%)	6	7	5	9·5	2	5	3·5	3·25	6·5	6·75	7	12·5	4·5	2·5	4	7·25	1·75	4
Intermediate (polychromatic) normoblasts (%)	49·5	44·5	45·5	42	25·75	49·5	46	12·5	32·5	31	29·25	46·75	50·5	4	45	41·5	47·75	51·5
Late (pyknotic) normoblasts (%)	42·5	46·5	46·75	45	25	41·5	48·5	15	57	22·5	38	38·5	44	8·5	44·25	38	49	42·75
Early (basophil) megaloblasts (%)	0	0	0	0	1	0	0	9·5	0	2·5	1	0	0	11·25	0	0·5	0	0
Intermediate (polychromatic) megaloblasts (%)	0	0	0	0	4	0·25	0	29·5	0	7	6	0	0	51·75	0·25	0	0	0
Late megaloblasts (%)	0	0	0	0	6	0·5	0	6·5	0	4	4·25	0·25	0	10	0·25	2	0	0
Transitional erythroblasts (%)	0	0	0·25	3	28	2·25	0	18·75	0	22	12	0·5	0·5	10	4	7·5	0	0·5

* After second injection of 1 mg. vitamin B_{12}.

erythroblast, recently described by Israëls (1951), and also by Dacie and White (1949) in their review, under the name of "intermediate megaloblast." As this term would lead to obvious confusion with the ripening frank megaloblast in the classification adopted in this study we have used the term "transitional erythroblast." These cells have appearances, especially in the nuclear chromatin, that are intermediate or transitional between those of a frank normoblast and a frank megaloblast.

The red-cell precursors in some of these marrows, both before and after treatment, were also counted, following the simpler classification suggested by Davidson *et al.* (1942). With this method it was found that gross megaloblastic change, and the alterations in the marrow 24–48 hours after injection described by these authors, were easily detected, but that lesser though definite megaloblastic changes were not revealed in such a classification. Examples of five treated and one initial marrow counted in this way are given for comparison (see Table II).

TABLE II.—*Differential Counts of Red-cell Precursors in Marrow Following Classification of Davidson et al. (1942)*

Patient	Days from Injection	Type I %	Type II %	Type III %	Type IV %
2	116	0·5	5·5	44·0	50·0
3	107	1·5	12·0	38·5	48·0
4	76	0·5	8·0	47·5	44·0
8	95	1·5	9·0	38·0	51·5
9	150	3·0	16·0	38·5	42·5
13	Initial untreated	33·5	32·5	24·0	10·0

Results

(1) Peripheral Blood

Erf and Wimer (1949) concluded from studies in four untreated patients that, in pernicious anaemia in relapse, remission could be maintained for 50–100 days with doses of 50–100 μg. vitamin B_{12}. This amount, however, was not always given in a single dose, and their criterion of remission was apparently symptomatic only, for in none of their patients was a red-cell count of over 4 millions recorded. In the patient followed for the longest period (114 days) the peak red-cell response was only 3.9 millions on the eighty-sixth day after a 50-μg. injection, and the red cells numbered only 3.2 millions and the haemoglobin was 68% on the 114th day. This is not surprising, as Ungley (1949a) found that the amount of vitamin B_{12} required (in divided and regular dosage) to raise the red cells to over 4.5 millions (that is, to complete remission) in 32 patients varied from 15 to 140 μg., and the time 15 to 118 days. Erf and Wimer also found that one patient required repeated doses because of severe neurological symptoms, persisting in spite of haematological improvement. They studied the effect of single doses of 32 μg. given to patients in remission for periods up to 140 days; but again their criteria for remission are vague, and the highest red-cell count recorded in these patients was 4.17 millions, the majority of counts being considerably lower.

Of the 15 patients of our series, 11 had complete remissions of varying duration following the injection of 1 mg. vitamin B_{12}, and one (No. 13) is still in the stage of improvement at the time of writing. One patient (No. 11) with subacute combined degeneration had to be given further injections at the end of six weeks because of neurological relapse; another (No. 4) did not achieve a higher red-cell count than 4.25 millions after the first injection, although remission was complete in other respects and was entirely satisfactory after the second injection of 1 mg., given on relapse at 128 days; while a third (No. 10), a man of 78 with a recent history of infective hepatitis and evidence of hepatic dysfunction, after an initial satisfactory response relapsed in 81 days. To date, eight patients have been followed till they showed signs of relapse after a first injection. In these, the time taken for relapse to show in the peripheral blood varied from 81 to 253 days. The short duration of response in patient No. 10 (81 days) may be due to defective storage of vitamin B_{12} in a damaged liver. Of the remaining patients, one (No. 2) is normal in blood and marrow nearly 12 months (358 days) after his single injection; another (No. 9) has normal blood findings after 251 days; while the four most recent patients have normal or improving blood at the end of 12 weeks.

Seven of the relapsed patients (Nos. 1, 3, 4, 5, 6, 7, 8) have been given a second injection of 1 mg. vitamin B_{12} at a time when the blood deficiency was slight. Patient No. 1 showed signs of relapse only after 348 days following this second dose, patient 3 after 192 days, patient 4 after 149 days, and patient 5 a probable relapse after 142 days. The others are still in remission at time of writing, 6–12 weeks after the second dose.

(2) Marrow

Mollin and Dacie (1950) found that to maintain a normoblastic marrow for 15 days after a single injection, doses as high as 30–40 μg. of crystalline vitamin B_{12} are required. With smaller doses, "average satisfactory" red-cell responses occur, but the marrow is megaloblastic before the end of 15 days. They emphasize the significance of "intermediate" (transitional) cells and the great sensitivity of these marrow changes, which vary in degree according to the severity of vitamin-B_{12} deficiency, of which they are the most delicate index. In this series (see Table I) three marrows, in different patients, were found to be completely normoblastic at intervals of 69, 92, and 358 days from the first injection, while three others, at intervals of 82, 95, and 150 days, showed changes from normoblastic haemopoiesis so slight as to be doubtful and negligible. Two further marrows were entirely normoblastic 93 and 98 days after the second injection of 1 mg. vitamin B_{12}, given on the first sign of relapse. Of the remainder examined after the initial dose, two showed very obvious megaloblastic change after 81 and 137 days, the first of these being the patient (No. 10) with hepatic insufficiency; while six showed minor but significant changes—from 3% to 35% of abnormal red-cell precursors—at 76, 86, 95, 107, 110, and 115 days after injection.

In all of these last six patients the clinical state and peripheral blood were normal (or, in the case of patient 13, still improving) at the time of the marrow examination, and a point of interest is the time that passed after the discovery of small though definite marrow abnormalities before signs of relapse became evident in the peripheral blood. In four of these patients the lag period between marrow and blood relapse was 43, 52, 72, and 55 days; the two others, more recent patients, have yet to show relapse in the blood. The two patients with a time-lag between marrow and blood abnormalities of 72 and 55 days defaulted for a while in attendance, else the interval might have been shorter. In spite of this it would appear that indications of megaloblastic haemopoiesis may be found in the marrow 40 to 50 days before any change is discovered in the blood. This is in accordance with the opinion of Mollin and Dacie (1950), that marrow changes are the most sensitive index of vitamin-B_{12} lack. In seven patients with normoblastic marrows (eight examinations) on follow-up, the time elapsing in two before blood relapse was discovered was 255 and 86 days, in a third (patient 5) 63 and 44 days, while four (2, 9, 14, 15) are still in remission (see Table I).

(3) Clinical and Neurological State

The general symptoms associated with anaemia improved in every patient with the improvement in the blood. Except in patients 10 and 11, there was no serious complicating disease. Only one patient (No. 7) complained of slight lassitude at the time when relapse was discovered in his blood. The others continued to feel normal. With one important exception (No. 11), none of these patients showed any evidence of subacute combined degeneration, either initially or while under observation, after one injection of 1 mg. vitamin B_{12}. Three (Nos. 3, 4, 8) had slight initial paraesthesiae confined to the tips of fingers or toes, and three

(Nos. 4, 7, 8) had initial sore tongue. These symptoms had complete relief. One patient (No. 15) had a severe stomatitis, which had resisted many forms of treatment but improved rapidly after the injection. Only one patient (No. 1) developed slight paraesthesiae while under observation, at a time when the blood showed evidence of relapse eight months after the injection. The symptoms disappeared after the second injection and did not return within 49 weeks.

Summary

Fifteen patients with untreated pernicious anaemia were given a single parenteral dose of 1 mg. of vitamin B_{12} and followed until relapse. The clinical state, blood, and marrow remained normal in one case for as long as 358 days after such a dose, but the earliest relapse occurred in 128 days, excluding one case with hepatic insufficiency where it occurred at 81 days.

The marrow showed minor signs of reversion to megaloblastic haemopoiesis 40–50 days before there was any sign of relapse clinically or in the blood.

No untoward neurological or other clinical symptoms were encountered in any patient with initially uncomplicated pernicious anaemia, but the one patient in the series with subacute combined degeneration had to have intensive treatment resumed at the sixth week because of neurological deterioration.

While of theoretical and practical interest, these findings do not justify, without further trials, the routine treatment of pernicious anaemia by 1 mg. doses of vitamin B_{12} at long intervals.

We would gratefully acknowledge the assistance given to us by our colleagues in Dundee General Hospitals, in particular Professor Ian G. W. Hill for permission to treat six patients admitted to his wards in Maryfield Hospital. We are indebted to Dr. H. M. Walker, of Glaxo Laboratories Ltd., for the supplies of vitamin B_{12} used in this study.

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The renaming of Bristol's new health centre after Dr. William Budd will keep alive the memory of a great general practitioner and a pioneer epidemiologist. Budd was one of the first to distinguish between typhoid fever and typhus, and his views on public sanitation, particularly on the importance of a pure water supply, were well ahead of his times. In 1841 Bristol had been declared by a Government commission "the third most unhealthy town in England," surpassed only by Liverpool and Manchester. There was indeed scope in Bristol for Budd's genius. During the 1849 cholera epidemic he recommended rational methods of prevention—the disinfection or destruction of dejecta and fomites, and the provision of pure water. A curious and little-known incident of Budd's later life is recorded in Dr. E. W. Goodall's book, *William Budd* (Arrowsmith, Bristol). Budd was well liked and respected by his colleagues, but once he incurred their severe censure. An article on scarlet fever, somewhat critical of current medical practice and over his own name, appeared in the *Bristol Times and Mirror* the day before it was published in the *British Medical Journal*. A meeting of the Faculty at Bristol, held in Budd's absence, declared this to be "inconsistent with professional propriety."

RENAL CIRCULATION AND CARDIAC OUTPUT IN "LOW-OUTPUT" HEART FAILURE AND IN MYXOEDEMA

BY

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It has been shown in a previous paper (Davies and Kilpatrick, 1951) that the cardiac output, the renal blood flow, and the glomerular filtration rate are reduced in congestive heart failure due to chronic rheumatic heart disease ("low-output" heart failure): the renal blood flow is reduced to a greater extent proportionately than the cardiac output and glomerular filtration rate. Merrill (1946) and Mokotoff, Ross, and Leiter (1948) postulated that retention of salt in low-output heart failure results from a low glomerular filtration rate in association with normal tubular reabsorption, but evidence has been adduced (Davies and Kilpatrick, 1951; Davies, 1951) which suggests that, although low glomerular filtration rate may be a contributory factor in salt retention, increased tubular reabsorption is more important.

The finding by Corcoran and Page (1947) of low renal clearances in two patients suffering from myxoedema suggested the present study, which is a comparison of the renal circulation, the cardiac output, and the ability to excrete salt in patients suffering from rheumatic heart disease and patients suffering from myxoedema. The former required regular administration of mercurial diuretics or severe restriction of salt intake in order to remain free of oedema. In addition, one patient with mitral stenosis *and* spontaneous myxoedema has been studied.

Normal standards for renal clearances were established in 14 healthy persons, and normal values for cardiac output were obtained from the work of McMichael and Sharpey-Schafer (1944).

Methods

The methods employed for the measurement of glomerular filtration rate (inulin clearance), renal plasma flow (*para*-aminohippuric-acid clearance), and renal blood flow $\left(\frac{\text{Renal plasma flow} \times 100}{100 - \text{Haematocrit}}\right)$ have been described previously (Dick and Davies, 1949; Davies and Kilpatrick, 1951). The validity of *para*-aminohippuric-acid clearance as a measure of renal plasma flow in patients suffering from myxoedema has not been established by determination of the concentration of *para*-aminohippuric-acid in renal venous blood. Cardiac output was measured by the methods of McMichael and Sharpey-Schafer (1944). The ability to excrete salt was measured by observing the effect of a diet containing 10 g. of salt and 1,500 ml. of fluid daily on the patients' weight.

Results

The findings in normal subjects, in patients with rheumatic heart disease, in patients with myxoedema, and in the single patient with both diseases are recorded in Tables I, II, and III.

TABLE I.—*Renal Clearances in 14 Normal Subjects*

	Range	Average
Glomerular filtration rate (ml. per minute)	119–174	145
Renal plasma flow (ml. per minute) ..	540–817	645
Renal blood flow (ml. per minute) ..	981–1,483	1,177

TABLE II.—*Renal Circulation and Cardiac Output*

Case No.	Sex	Age	G.F.R. (ml./min.)	R.B.F. (ml./min.)	O_2 Consumption	B.M.R.	A–V O_2 Diff. Vols.%	C.O. litres/min.
Patients with Low-output Heart Failure								
1	M	42	51	323	275		9·5	2·8
2	F	44	53	510	270		9·7	2·8
3	F	48	60	330	280		7·7	3·6
4	F	47	77	367	—		—	—
5	F	67	52	520	—		—	—
6	M	41	62	450	—		—	—
7	F	38	94	483	275		7·3	3·8
8	F	15	56	487	200		8·1	2·4
9	F	38	80	490	255		8·2	3·0
10	M	27	78	429	250		6·05	4·1
Patients with Myxoedema								
11	F	56	72	435	140	−35%	4·75	3·0
12	F	60	55	560	150	−22%	4·5	3·3
13	F	67	81	633	135	−20%	5·0	2·7
14	F	47	62	354	101	−44%	4·3	2·7
15	F	46	48	467	—	−35%	—	—
16	F	41	90	520	—	−36%	—	—
Patient with Rheumatic Heart Disease and Myxoedema								
17	F	43	56	320	134	−31%	—	—

G.F.R.=Glomerular filtration rate. R.B.F.=Renal blood flow. C.O.=Cardiac output.

TABLE III.—*Effect of a Diet Containing 10 g. of Salt Daily on Body Weight*

Case No.	G.F.R. (ml./min.)	R.B.F. (ml./min.)	No. of Days on Diet	Initial Weight (kg.)	Final Weight (kg.)
Patients with Chronic "Low-output" Heart Failure					
1	51	323	5	57·0	60·8
4	77	367	6	50·0	54·3
5	52	520	6	60·4	65·0
6	62	450	6	48·6	51.8
Patients with Myxoedema					
11	72	435	12	77·0	77·1
12	55	560	12	54·7	55·1
14	62	365	9	48·8	49·7
Patient with Mitral Stenosis and Spontaneous Myxoedema					
17	56	320	16	61·5	61·6

G.F.R.=Glomerular filtration rate. R.B.F.=Renal blood flow.

Renal Circulation

(a) *Glomerular Filtration Rate*

Normal subjects .. 119–174 ml./min.; Average, 145 ml./min.
Rheumatic heart disease .. .. 51–94 " " 66 "
Myxoedema .. .. 48–90 " " 68 "
Rheumatic heart disease and myxoedema .. 56 "

(b) *Renal Blood Flow*

Normal subjects .. 981–1,483 ml./min.; Average, 1,177 ml./min.
Rheumatic heart disease .. .. 323–520 " " 439 "
Myxoedema .. 354–633 " " 495 "
Rheumatic heart disease and myxoedema .. 320 "

Cardiac Output

(a) *Oxygen Consumption*

Normal subjects* .. Average normal adult, 240 ml./min.
Rheumatic heart disease .. .. 200–280 ml./min.; Average 258 ml./min.
Myxoedema .. .. 101–150 " " 131 "
Rheumatic heart disease and myxoedema .. 134 "

(b) *Arteriovenous Oxygen Difference*

Normal subjects* .. 3.0 –5.2 vols.%; Average 4.0 vols.%
Rheumatic heart disease .. .. 6.05–9.7 " " 8.0 "
Myxoedema .. .. 4.3 –5.0 " " 4.6 "

(c) *Cardiac Output*

Normal subjects* .. 4 –8 l./min.; Average 5.3 l./min.
Rheumatic heart disease .. .. 2.4–4.1 " " 3.2 "
Myxoedema .. .. 2.7–3.3 " " 2.9 "

(d) *Cardiac Output per 100 ml. of Oxygen Consumed*

Normal subjects* .. Average 2.2 l./min.
Rheumatic heart disease .. .. " 1.2 "
Myxoedema .. .. " 2.2 "

Salt Excretion

All the patients with rheumatic heart disease required severe restriction of salt intake or mercurial diuretics at varying intervals in order to remain free of oedema, whereas none of the patients with myxoedema showed pitting oedema while on an ordinary diet. The administration of a diet containing 10 g. of salt and 1,500 ml. of fluid daily caused a rapid increase of weight and a rise of venous pressure in the patients with rheumatic heart disease, but these changes did not occur in the patients suffering from myxoedema or in the single patient suffering from both diseases (Table III).

Discussion

These observations show that in two small groups of patients suffering from low-output heart failure or myxoedema the glomerular filtration rate, renal blood flow, and cardiac output were low, and that the values obtained in the two conditions were of the same order. There were, however, important differences. In the patients with myxoedema the capacity to excrete ingested salt and water was normal, whereas it was severely impaired in the patients with low-output heart failure. Moreover, the low cardiac output of myxoedema was associated with a normal arteriovenous oxygen difference, and the cardiac output per unit of oxygen consumed was within normal limits, which suggests that the circulation was fulfilling the tissue requirements for oxygen in a normal manner. However, a normal arterio-mixed-venous oxygen difference does not necessarily mean that the arteriovenous oxygen difference of individual organs is also normal.

The difference in capacity to excrete salt suggests several possible explanations. In low-output heart failure retention of salt may be due to a diminished glomerular filtration rate in association with normal tubular reabsorption, or to increased tubular reabsorption alone, or to a combination of these two factors. If a glomerular filtration rate of the order found in these two groups of patients causes salt retention in the presence of normal tubular reabsorption, it follows that tubular reabsorption is below normal in myxoedema. If, on the other hand, salt retention in low-output heart failure is wholly or partly due to increased tubular reabsorption, then in myxoedema tubular reabsorption may be normal or below normal. That some aspects of tubular function are depressed in myxoedema is shown by the presence of a low maximum tubular excretory capacity (Corcoran and Page, 1947). Depression of tubular reabsorption of salt may be due either to local changes in the cell or possibly to diminished hormonal stimuli, since Zarrow and Money (1949) have shown that experimental hypothyroidism causes atrophy of the adrenal cortex.

The findings reported here may explain to some extent the old-established clinical observation that induced myxoedema prevents or diminishes oedema in chronic heart failure. It was assumed (Blumgart *et al.*, 1933) that clinical improvement resulted from diminished cardiac work, but

*After McMichael and Sharpey-Schafer (1944).

Sharpey-Schafer (1946) found that myxoedema artificially induced by thiouracil in patients with chronic heart failure did not lead to a change in the work of the heart (cardiac output × mean blood pressure).

It seems possible, therefore, that the beneficial effect of induced hypothyroidism is, in part, the result of changes in the tubular reabsorption of salt and water. It is of interest, in this respect, that the patient who suffered from both mitral stenosis and spontaneous myxoedema was able to excrete salt and water normally although her renal clearances were at the same level as those of patients with low-output heart failure.

Summary

The renal circulation and the capacity to excrete salt have been studied in small groups of patients suffering from myxoedema or chronic rheumatic heart disease, and in one patient suffering from both conditions. In some patients from each of the two groups the cardiac output has been measured.

The glomerular filtration rate and renal blood flow were reduced to approximately the same extent.

In spite of the similar renal circulatory changes the patients with myxoedema were able to excrete salt and water, whereas that function was seriously impaired in the patients with rheumatic heart disease.

One patient with mitral stenosis and spontaneous myxoedema had renal clearances of the same order as the other patients studied, but was able to excrete salt and water.

The cardiac output was low in both groups, but, whereas the arteriovenous oxygen difference and the cardiac output per unit of oxygen consumed were abnormal in the patients with rheumatic heart disease, these values were normal in the patients with myxoedema.

The significance of these findings is discussed.

We are indebted to Professor C. H. Stuart-Harris for his help and for the opportunity of studying patients under his care, and to Dr. M. W. A. Gatman for many biochemical estimations.

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An important service rendered by Post Office wireless stations on the coasts of Britain is the transmitting of medical advice to ships at sea. In the absence of a ship surgeon, illnesses among the ship's company are generally dealt with by the captain, so far as he is able, with the aid of the ship's medical chest. In serious cases where the captain feels that a doctor's opinion is desirable he may forward particulars to a coast station by radio. If suitable equipment is installed in the ship it is possible for the captain and the doctor to speak directly to each other by a combination of the radio link and the normal telephone system. These messages are sent either in plain language or in a special code devised to overcome language difficulty when dealing with foreign ships. During 1951, 469 medical messages were handled by Post Office coast stations.

THE TREATMENT OF LUMBAR INTERVERTEBRAL DISK PROTRUSION

AN ASSESSMENT OF CONSERVATIVE MEASURES

BY

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So common has become the diagnosis of intervertebral disk protrusion as a cause of backache and sciatica that it is important to emphasize the small part that operation plays in the treatment of this disorder. O'Connell (1951), in a review of 500 cases treated by operation, made it clear that most of his patients were referred to him only because long periods of conservative treatment from general practitioners, physicians, neurologists, or orthopaedic surgeons had failed. Of all patients seen in his clinic, he considered that less than 20% needed operation.

In a disorder with a tendency to natural cure a patient may receive many different lines of treatment while the natural history of the condition unfolds. The success or failure of such treatment is too often judged on a basis of trial and error. The purpose of this review is to assess, so far as is possible, the results of the various forms of conservative treatment carried out in the orthopaedic department of St. Bartholomew's Hospital over five years.

Material and Results

In all, 500 unselected patients have been observed for a period of not less than 18 months from their initial treatment. They attended the orthopaedic department between 1946 and 1951 with symptoms and signs giving rise to the diagnosis of lumbar disk protrusion. This number is only a very small fraction of all the patients with lumbar and sciatic pain who attended the hospital in that time. Those with backache but without evidence of lumbar root involvement or neurological disturbance have been excluded from this series. Of the total number, 314 were men and 186 women. Two patients have died since discharge from hospital—apparently from causes unconnected with their spinal condition; five recovered spontaneously while awaiting treatment.

The upset caused by disk protrusion is essentially subjective and the results of conservative treatment are therefore difficult to assess. In the accompanying Table the term "relieved" implies complete loss of pain and disability without recurrence during the period of review; "improved" indicates that the patient has been able to resume work or normal life. The number of patients completely relieved by treatment is very small when compared with O'Connell's (1951) figures for those treated by operation. But, as he himself said, patients requiring operation have suffered severe or prolonged disability and mild post-operative symptoms are unlikely to give cause for complaint. Conservative treatment, on the other hand, is given for all degrees of severity and rarely produces such dramatic changes as operation. Recurrence, moreover, is to be expected unless advice on such matters as the lifting of heavy weights without bending the spine and the avoidance of stooping is followed carefully.

Of the 500 patients, 406 were initially improved or relieved, and only 58 were considered eventually to require operation. Sixteen were not improved, but were deemed unsuitable for operation because of associated functional

disorders. A few were treated by epidural injection, but the number was too small to assess the value of this form of treatment.

Table of Results

Initial Treatment	Total	Relieved	Improved	No Initial Improvement	Recurrence	Ultimate Improvement with Conservative Measures	Operation
Rest in bed ..	123	15	72	36	33	26	43
Plaster jacket	71	14	38	19	19	33	5
Lumbo-sacral support ..	104	9	88	7	3	10	0
Manipulation	68	10	40	18	15	23	10
Exercises ..	129	34	81	14	11	25	0
Spontaneous recovery ..	5	5	—	—	—	—	—
Total ..	500	87	319	94	81	117	58

Methods of Treatment

Rest in Bed.—Complete rest in bed for at least three weeks, preferably in hospital, was advised when the symptoms were severe or of sudden onset and root tension signs well marked. Although more than half were relieved or improved, a quarter suffered recurrence of symptoms. All those failing to show initial improvement with rest were ultimately treated by operation, as were one-third of those whose symptoms recurred. Continuous leg traction was not used in this series.

Plaster Jacket.—This form of immobilization was used when rest in bed was indicated but economically impossible, or sometimes to prolong rest when improvement was slow. Lasting improvement was obtained by plaster alone in about half the patients treated. This corresponds with the findings of Durbin (1948). Jackets were initially applied in the position of the deformity and subsequently changed if necessary.

Lumbo-sacral Support.—Usually patients were fitted with supports when their symptoms were mild and when their lives and work involved activity which made recurrence probable. Old people, child-bearing housewives, and policemen were the commonest candidates for this form of treatment. Twice as many men as women were fitted with spinal supports. Experience showed that, once fitted, very few were able to leave off their instruments and most patients were content to depend on them indefinitely.

Spinal Manipulation.—Patients treated by this method fell into two groups. Of 15 patients with spasm and signs of root tension only three were relieved or improved, and 10 eventually came to operation; despite the alleged dangers of paraplegia (Goldthwait, 1911), in no cases were symptoms or signs made worse. During manipulation, movements were always carried out gently and flexion was avoided. Though manipulation is not now generally advocated for the acute type of case, it is interesting to read old case records of "sciatic scoliosis" in the days before the real cause of this condition was recognized. Though movements, including full flexion, were then always carried out strongly, there were apparently no disasters and some dramatic and lasting cures. Of the second group, those with stiff backs, little root involvement, and a long history of moderately severe symptoms, more than half were relieved or improved. In addition to those recorded as being treated primarily by manipulation in this series, 20 patients were not improved by physiotherapy or exercises until after manipulation had been carried out. They had already undergone several other forms of treatment.

Extension Exercises.—It has long been realized that no form of treatment is complete unless exercises to strengthen the extensor muscles of the spine are taught at the same time. In an acute attack exercises are often not at first possible, since any exertion aggravates the pain. In this series, 129 patients with mild symptoms were primarily treated by extension exercises with or without some other form of physiotherapy. It will be seen that over 90% of the patients were improved or relieved without any other treatment. O'Connell (1951) considered that exercises should be designed not only to strengthen the extensor muscles but also to restore full mobility.

Discussion

The number of patients with disk protrusion attending hospital to-day far exceeds those treated in the years covered by this review, no doubt because both doctors and patients are now "disk-conscious." Accurate diagnosis having been established by investigation, the main problem is to select the right treatment at the right time and reduce the period of disability.

The present investigation shows that for patients with severe root involvement the correct advice should be complete rest followed by graduated exercises. For mild symptoms, early institution of back exercises and physiotherapy is probably the right treatment. The majority of cases, however, lie between these extremes, and it is in these, with moderate disability, that the decision regarding immobilization is more difficult.

The effect of prolonged immobility may lead to "fibrous ankylosis" of the spine at the affected level (Crisp, 1945), while the protrusion becomes organized; or immobility may sooner or later promote adhesions between disk tissue and lumbar roots (as are often seen at operation) and in the periarticular tissues. If the protective spasm that so often obliterates the normal lumbar curve becomes fixed by such adhesions after long immobilization, the spinal extensor muscles will no longer be able to act at a mechanical advantage. As a result these muscles will waste and lose tone in the same way as the quadriceps when knee extension is lost. As the spine thus loses its natural brace a vicious circle will be brought into being, with increasing liability to strain and recurrent symptoms. This is the state of affairs for which manipulation, aiming to restore extension and rotational mobility, may be expected to be of most value. The presence of these adhesions becomes evident when passive extension of the spine in the prone position causes pain during routine examination. If their presence is not recognized many patients may find themselves with the burden of a supporting corset which will only partially relieve their symptoms and which they will never be able to discard.

Of the patients in this series, 75% were between 30 and 50 years of age; 15% were under 30, and only 10% over 50. Of those fitted with spinal supports nearly half were under 40. Though it is clear from the records that young patients were treated in this way only to allow them to carry on their work, it is suggested that generally these instruments should be reserved for old people with degenerative changes in their lumbar spines. There would seem to be a grave danger to-day that large numbers of active men and women are being condemned more or less indefinitely to these corsets, when more active measures might give greater relief.

Summary

A review is made of a series of 500 unselected cases of lumbar intervertebral disk protrusion observed over a period of not less than eighteen months from the starting of treatment.

An attempt has been made to assess the value of, and indications for, the various measures used in conservative treatment over a five-year period.

I should like to thank Mr. S. L. Higgs, Mr. H. Jackson Burrows, and Mr. W. D. Coltart for their help and permission to make use of case records of their patients, and Mr. J. E. A. O'Connell for his kind advice.

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Medical Memoranda

Subacute Bacterial Endocarditis Caused by Str. haemolyticus Group H

Subacute bacterial endocarditis has been studied in great detail, particularly since the introduction of penicillin therapy. The responsible organisms are usually those found in the upper respiratory tract, with *Streptococcus viridans* predominant (Niven and White, 1946; Cates and Christie, 1951), and it is generally agreed that the mouth and pharynx constitute the common sites from which the cardiac infection arises, often as a result of local trauma (Jones *et al.*, 1947).

The following case is typical in most respects, but, as the causative organism proved to be *Streptococcus haemolyticus* Group H it is thought to be worthy of record.

CASE REPORT

A female shop assistant aged 20 had a history of rheumatic fever in childhood. In March, 1951, she had a tooth extracted and within a few days felt tired and listless; her condition slowly deteriorated and she had been in bed with a swinging temperature for some four weeks before admission to hospital on April 28.

On examination she presented the usual signs of subacute bacterial endocarditis—namely, pyrexia, valvular lesions, Osler's nodes, and an enlarged spleen. Blood cultures were made on April 28 and 29 and yielded a growth of *Str. haemolyticus* (approximately 200 colonies per ml.). This organism proved to be sensitive to penicillin, streptomycin, aureomycin, and chloramphenicol. *Beta* haemolysis was persistently produced on blood-agar plates, and, as a reaction was not obtained with the usual type sera, it was sent to the Colindale Reference Library, where it was found to be *Str. haemolyticus* Group H.

A routine course of penicillin (2,000,000 daily for 42 days) was begun on April 29, and the clinical result was very satisfactory; blood cultures prepared during and after the course were sterile.

COMMENT

This appears to be the first case of subacute bacterial endocarditis in which *Str. haemolyticus* Group H has proved to be the responsible organism. Porterfield (1950) carried out a comprehensive investigation of a number of streptococci isolated from cases of subacute bacterial endocarditis and found that some strains, although non-haemolytic, gave the same biochemical and serological reactions as *Str. haemolytic* Group H. He consequently thought that these strains were non-haemolytic or *viridans* varieties of Lancefield Group H. He also demonstrated that these organisms were similar to *Streptococcus sanguis* (s.b.e.) type 1, which had been isolated from endocarditis cases and described in detail by White and Niven (1946). It is interesting to note that Loewe and his colleagues (1946) reported that, although *Str. s.b.e* strains were sensitive *in vitro* to penicillin, the clinical response to penicillin therapy tended to be unsatisfactory in endocarditis cases caused by these organisms.

Group H *Str. haemolyticus* was originally isolated by Hare (1935) from the throats of normal individuals, and later (Hare and Maxted, 1935) from faeces; he then thought it improbable that these strains ever caused serious human infections. Although giving complete haemolysis on blood-agar plates, a soluble haemolysis was not formed, and Hare believed that Group H strains might have been the same as some of the strains described earlier as pseudo-haemolytic streptococci. It is now accepted as a non-pathogenic member of the upper respiratory flora (Wilson and Miles, 1946; Swift, 1948). *Str. haemolyticus* Group H thus occupies a role comparable with *Str. viridans*, which is the organism most often responsible for subacute bacterial endocarditis.

In the above case several unsuccessful attempts were made to isolate Group H haemolytic strains from the gums, throat, and nasopharynx of the patient, but unfortunately these efforts were not started until the late stages of penicillin therapy. It does, however, seem highly probable that the organisms gained entrance into the blood stream at the time of the tooth extraction and then settled on the heart valves previously damaged by rheumatic fever.

It is a pleasure to thank Dr. N. Kletts for the clinical details of the case and the Colindale Reference Laboratory for typing the strain.

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Carcinoma of Cardiac Portion of the Stomach

Carcinoma of the stomach is a gloomy disease. There is no doubt that so few cases are truly operable when first seen because symptoms are slight or absent until the disease is advanced. Barium meal *x*-ray examination and gastroscopy are most useful in carcinoma of the body or pylorus. In carcinoma of the cardiac end, gastroscopy and oesophagoscopy are of little use. A barium meal is not seen at its best here either. It may not be possible to visualize a growth in this area, but, lest it be thought that the diagnosis is too difficult, I should add that this is the area most likely to produce symptoms. The nearer the growth is to the cardiac orifice the more likely is the patient to complain of difficulty in swallowing. It may not be very severe or apparently present all the time, nor may it be in the so-called cancer age group, but despite this it may be the first symptom of a carcinoma.

During 1950 I operated upon 16 cases of carcinoma of the stomach—seven were of the cardiac end and are discussed in detail, and nine were of the body and pylorus, three being operable.

CASE REPORTS

Case 1.—A married woman aged 34 attended the out-patient department in December, 1949, with a three-months history of dysphagia and pain when she swallowed solids but not liquids. Otherwise she was quite well. Barium meal: Diagnosis of cardiospasm. Hb, 64%. Belladonna and other antispasmodics gave no relief. I saw her late in January, 1950, and was struck by the pain and loss of weight; but there were no signs on examination. She was admitted on March 20 and oesophagoscopy was performed on March 22. Nothing definite was detected, but as the mercury bougie would not go down she was *x*-rayed again and an apparently typical cardiospasm was seen as before. Despite this her condition worsened and laparotomy was decided upon; her condition was desperate. At laparotomy on April 12 a large growth was found at the cardia, possibly oesophageal; there were no secondaries. She was quite unfit for anything except a jejunostomy, which was performed. She improved greatly. On May 3 a transthoracic approach was made: the growth still appeared to be mainly oesophageal. A combined incision in abdomen and thorax was made, splitting the diaphragm, and most of the stomach and the lower 2 in. (5 cm.) of oesophagus were removed. Direct anastomosis in

the chest was performed, and the chest closed without drainage. Uninterrupted recovery. Jejunostomy tube removed on May 15; closed May 20. Discharged May 22. When last seen she was well and enjoying food. Pathological report: adenocarcinoma of cardiac orifice; no secondary deposits found in distant glands.

Case 2.—A man aged 66 was seen in the out-patient department on April 1, 1950, complaining of epigastric pain and flatulence for four years, and loss of weight, difficulty in swallowing, phlegm, and chronic cough for one year. He was admitted on May 8. A barium meal showed carcinoma of fundus of stomach. At operation on May 10 a large tumour was found arising from lesser curve just below the cardiac orifice; no secondaries. Left lobe of liver mobilized and total gastrectomy, including spleen, performed from below diaphragm. Direct oesophago-jejunostomy performed and also jejunostomy. Getting on very well. Swallowing semi-solids until May 16, when he collapsed and died. Post-mortem report: massive pulmonary embolus; no secondaries; operation site entirely satisfactory. Pathological report: adenocarcinoma of stomach.

Case 3.—This patient, aged 22, had a crust of bread stick in the gullet on December 25, 1949. Pain at lower end of sternum was relieved by a drink. This had occurred once before, so on January 11 a barium-meal examination was made. It showed spasm at cardiac end of stomach, ? small ulcer present. Now appeared quite well. On March 8 a barium meal was practically normal; no symptoms. Later this month further sticking of food occurred, which got worse. After admission on May 22 an urgent barium meal showed filling defect at cardia. Laparotomy on June 13 revealed an inoperable growth of cardiac end of stomach with massive local spread. The patient died on July 31, despite use of H 11. Pathological report: omental secondary; spheroidal-cell carcinoma. Post-mortem report: probably not carcinoma, but fibrosarcoma.

Case 4.—This patient, aged 35, complained of pain on swallowing in September, 1949, and was treated elsewhere for ulcer of larynx. Gradually increasing difficulty in swallowing occurred, with loss of weight, pain, and sweating at night. On admission to a medical ward on May 1, 1950, the patient was thin and ill. There was no occult blood. The Hb was 78%. An *x*-ray film showed a large filling defect of lower end of oesophagus. Oesophagoscopy revealed no definite new growth. Radiotherapy had little effect. Nocturnal temperature and pain persisted. Although it seemed hopeless thoracotomy was performed on August 15. It revealed pleural effusion, glands in hilum of lung, a growth apparently from stomach, not oesophagus, quite inoperable, invading diaphragm and liver. The patient died on September 11. Post-mortem report: adenocarcinoma of stomach; massive secondary growths in liver and elsewhere; the latter secondaries presumably accounted for the persistent nocturnal temperature.

Case 5.—The patient, aged 35, was admitted to a medical ward on July 27, 1950, complaining of retrosternal pain and regurgitation of food for three months. At first the pain was slight, but got worse and was followed by vomiting. The patient lost 2 st. (12.7 kg.) in weight and on admission could swallow only liquids. Examination revealed extreme wasting but no other signs. An *x*-ray film showed no growth at cardia but some delay. I saw the patient on August 9 and laparotomy was performed the same day. Carcinoma of the cardiac orifice was present; no apparent secondaries; fit only for a jejunostomy. By August 22 the condition had greatly improved so further operation was justified. A combined thoracic and abdominal approach, splitting diaphragm, was made. The growth was very adherent, but the whole of the stomach and spleen and part of the diaphragm were removed in one piece. The right pleura must have been accidentally opened, as a tension pneumothorax developed and the heart stopped. This was overcome by packing the wound deeply, aspiration of the chest, and cardiac massage. The operation was then quickly completed as in Case 1. The patient was fairly well but did not regain consciousness, and died next morning. Post-mortem report: poorly differentiated adenocarcinoma of stomach; considerable direct spread; secondary deposit in ovary; suture line was not entirely satisfactory.

Case 6.—The patient, aged 72, was admitted on October 18, 1950, complaining of loss of weight, weakness, and breathlessness. The appetite was poor; there was no vomiting. Food and alkalis gave relief. On examination the patient was pale, with poor air entry to chest; normal abdomen; Hb, 40%; no free acid. A barium meal showed no evidence of new growth in stomach. Laparotomy revealed an inoperable carcinoma involving the upper third of the stomach; direct spread posteriorly; many secondary deposits. Pathological report on secondary nodule removed: adenocarcinoma, probably from stomach. The patient was discharged home on December 3.

Case 7.—A woman aged 44 was admitted to a medical ward on October 18, 1950, complaining of pain in the chest and epigastrium for four months, loss of appetite for six weeks, and occasional vomiting of watery froth. No relief from alkalis. Examination showed gross anaemia and loss of weight—she had weighed 18 st. (114.3 kg.) and had lost 4–5 st. (25.4–31.8 kg.)—abdomen, no mass felt. Occult blood ++; Hb, 34%; test meal, normal acid curve; barium meal, N.A.D. At laparotomy on December 13 an enormous tumour arising from the cardia was seen. It was apparently operable, so the incision was converted to a combined thoraco-abdominal one, splitting the diaphragm. Total gastrectomy, including spleen and part of pancreas, oesophago-jejunostomy, entero-anastomosis, and jejunostomy were performed. Operation specimen: large growth but little ulceration. The patient made an uninterrupted recovery and was discharged on January 6, 1951. Her haemoglobin was 90%, she was eating a normal diet, but had no appetite. Pathological report: anaplastic undifferentiated carcinoma of stomach; invasion of lymphatic nodes present.

DISCUSSION

The youth of the patients is notable. Out of seven, one was aged 22, three were in the thirties, and one was in the forties. This, coupled with the one prevailing symptom—difficulty in swallowing—makes one's mind run to cardiospasm. Provided one thinks of carcinoma as a likely cause of difficulty in swallowing at any age the main danger is ruled out. Vomiting is not so characteristic as in cardiospasm, but wasting and particularly anaemia are more marked. Occult blood may be negative in carcinoma and the fractional test meal may show a good acid curve, so that these findings are not helpful if normal.

This is the most difficult type of growth to visualize radiographically, and attempts to do so must include pictures in the Trendelenburg position and may include the giving of a Seidlitz powder to produce gas in the stomach. Even so, an apparently normal picture may be produced. This is bad enough if the oesophagus does not appear dilated, but it may be made worse by having the characteristic goblet dilatation of cardiospasm. If such a case does not show temporary relief by amyl nitrite it must be suspect. Classically, the dilatation is greater in cardiospasm, but it is dangerous to rely on this alone. I have not found cardiospasm as common as carcinoma, but innocent stricture may occur. Both should show relief by dilatation with bougies. Temporary spasm may also occur from a small peptic ulcer just above or below the cardiac orifice; these should clear up quickly, and if they do not must be suspected of being malignant. When in doubt, surgical exploration is the correct procedure. While a one-stage operation is ideal, if it had been attempted in Case 1 or Case 5 there could have been only one result. Jejunostomy was here a life-saving measure. I also think it wise after a one-stage operation as in Case 7, as it allows immediate nutrition in these starving people without the worry of the anastomosis. I found that the Witzel type worked well and gave no trouble.

W. D. PARK, M.S., F.R.C.S.

Reviews

HISTORY OF NEUROSURGERY

A History of Neurological Surgery. Edited by A. Earl Walker, M.D. (Pp. 583; 152 figures. £4 11s. 6d.) London: Baillière, Tindall and Cox. 1951.

Neurosurgery: An Historical Sketch. By Gilbert Horrax, M.D., Sc.D (Pp. 135; 41 figures. £1 7s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952.

Dr. Earl Walker's book is a handsome work with many illustrations selected with skill and admirably reproduced. He has not only written well himself, but has managed his team of contributors skilfully. The history of operations on the skull and brain is traced onwards from the early trepanation for ritual or therapeutic purposes down to the present day. There are over 2,300 references, and, although this gives a clear indication of the wide scope of the work, it also suggests that many stories are only partly told. Naturally the Americans are more fully represented in the references than any other nations, but no one could complain of any intentional unfairness. The omission of Thorburn's name will strike a Briton as curious. It is not, it is hoped, too unkind to say that there are only sporadic opportunities for a book like this to show deep scholarship or penetfating insight into the minds and methods of the people discussed.

The book came about as a result of a series of seminars at Johns Hopkins on the development of the surgery of the nervous system. The level is therefore not too high yet not too low. The general plan has been to describe the changing trends in neurosurgery in chapters devoted to different subjects—technique, and the surgery of different regions or affections such as the hypophysis, infection, trauma, epilepsy, the peripheral nerves, sympathetic nervous system, and so on. Most of them are well done. An interesting feature is the series of thumbnail sketches of many of the great ones of the past—Horsley, Macewen, Cushing, Frazier, Dandy, von Bergmann, Krause, Puusepp, and others. In a historical work such as this the use of reference numerals instead of dates is singularly maladroit and is to your reviewer a major blemish, though others may be less irritated by it than he. However, an enormous amount of work has gone into the compilation of the book, and it would be most ungracious not to greet it with some warmth and to recommend it as an informative and enjoyable book.

By a coincidence a smaller book on the same subject has just appeared. It is from the pen of Dr. Horrax, now neurosurgeon-in-chief to the Lahey Clinic, formerly for so many years Harvey Cushing's trusted assistant, colleague, and friend. This is an admirable short account of most things that have happened in the development of neurosurgery from its origins in the days of uncertainty to the greater precision of to-day. The greater part of the book is devoted to what the author calls the "Pre-Horsley Period" and the "Neurosurgical Era." Dr. Horrax is completely equipped to tell the second story well, for he was with Cushing during the whole of his greatest period. The book has a logic and cohesion that will win it many friends. Like all Thomas books, it is perfectly produced.

GEOFFREY JEFFERSON.

TUMOURS OF THE SKIN

Tumors of the Skin: Benign and Malignant. By J. J. Eller, B.S., M.D., and W. D. Eller, M.D. Second edition, thoroughly revised and enlarged. (Pp. 697; 550 illustrations and 3 coloured plates. £5 5s.) London: Henry Kimpton. 1952.

This is the second edition of an important contribution to dermatological literature. It is comprehensive, well written, beautifully illustrated, and admirably produced. Tumours of the skin are accessible and should be diagnosed early, as the authors emphasize, and early treatment should result in cure. For this reason this work is of importance and interest to the general practitioner as well as the dermatologist. The excellent clinical descriptions of the wide range of lesions covered, histological details, and discussion of therapy are based largely on the authors' experiences. There is also adequate reference to historical aspects and to authoritative observations, and a good bibliography with each section.

In a work that is admirable throughout, special mention may be made of the section on precancerous dermatoses and the stimulating chapter on cutaneous surgery. Leukoplakia vulvae is not very satisfactorily discussed, and few medical men in Britain would use the term kraurosis or fully subscribe to the concepts of Berkeley and Bonney. In discussing the pyogenic granuloma and milker's nodes the authors might add a note on orf, contracted from sheep. They do not mention molluscum sebaceum, described by MacCormac in 1935, which has been much discussed in recent years. Carcinoma erysipelatodes is mentioned and illustrated under breast cancer, but its histology and significance are not indicated, nor is mention made of carcinoma telangiectaticum. The authors properly emphasize in the section on surgery the importance of incising the skin along the lines of cleavage. This might with advantage be indicated in the chapter on keloids as of importance in preventing keloid formation from surgical incisions. But these are minor points and do not detract from the high standard of the work, which will be welcomed by British dermatologists.

J. T. INGRAM.

CARDIAC PAIN

Cardiac Pain. By Seymour H. Rinzler, M.D., F.A.C.P. American Lecture Series 113. (Pp. 139; 13 illustrations. £1 7s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952.

It is a pleasure to recommend this little book to all who are concerned with the management of patients with cardiac pain, to any who are about to undertake therapeutic trials of new remedies for angina pectoris, to surgeons using any operative technique for relieving cardiac pain or for improving the coronary circulation, and to research workers interested in the nature of cardiac pain as such.

Dr. Rinzler is to be congratulated on producing a concise, well-written, nicely balanced, accurate monograph on an important practical subject. He reviews the history well, and gives an adequate discussion of the mechanism of cardiac pain and its somatic reference. The description of clinical features is competent, and 18 out of the 88 pages are devoted to differential diagnosis. He gives as much space to assessing the value of nearly all known medical treatments, including nitrites, xanthines, papaverine, alcohol, khellin, androgens, vitamin E, cytochrome C, artificial myxoedema, and nicotinic acid. Factual details are given throughout and conclusions are always fair. There is a helpful chapter on the place of surgery, including the minor procedure of local procaine blocking of trigger areas to relieve the somatic component of cardiac pain (such as the frozen shoulder syndrome). There is an extensive well-selected international bibliography (335 references), and there are a number of useful tables and sketches.

PAUL WOOD.

PHYSICAL MEDICINE

Physical Medicine and Rehabilitation for the Clinician. Edited by Frank H. Krusen, M.D. (Pp. 371; illustrated. £1 12s. 6d.) London and Philadelphia: W. B. Saunders Company. 1951.

In the preface to this book Krusen explains that it is based on a series of postgraduate lectures delivered by various specialists in branches of physical medicine. It comprises four main parts on, respectively, therapeutic applications, diagnostic applications, clinical aspects, and fundamentals of anatomy and physiology.

All the sections are thoroughly up to date. No effort has been made to keep alive outdated or traditional methods

of using electric currents or other therapeutic procedures; even such a time-honoured treatment as massage is critically and scientifically appraised. Similarly, modern ideas and tendencies are carefully analysed and discussed; thus in addition to informative chapters on present trends in electro-diagnosis, the claims of micro-wave diathermy and ultrasonics are carefully considered and impartially presented. The chapters on rehabilitation, physical and psychological, both in hospital and at home, are exceptionally well done and cover all clinical conditions from trauma and paraplegia to arthritis in which rehabilitation is needed. A particularly interesting chapter on rehabilitation in a general hospital is contributed by Howard Rusk.

Unlike other books on physical medicine this one is not particularly intended for the specialist in physical medicine or for the physiotherapist, although these will be well advised to read it. It is intended for the clinician, as its title indicates; he will learn not only where physical medicine can help him but also where it cannot.

This is a refreshing book on a much neglected subject. It is well set out, essentially readable, and can be strongly recommended.

WILLIAM TEGNER.

INTRODUCTION TO RADIOLOGY

Einführung in die Röntgenologie. By Professor G. F. Haenisch and Professor H. Holthusen. Fifth edition. (Pp. 521; 371 figures. M. 60.) Stuttgart: Georg Thieme. 1951.

This introduction to radiology is intended for those who mean to make radiology their life's work, and it very fully meets their requirements. The first half of the book is on the use of *x* rays in diagnosis. It opens with an account of the physical nature of *x* rays and of the apparatus used for their production and control. This is followed by a full account of their clinical use, profusely illustrated by examples of both normal and abnormal conditions. The various sources of error and the means by which these can be avoided are well discussed. The illustrations are superb and cover the whole field of diagnosis in abnormal conditions of the bones, of the intestinal, respiratory, and urinary tracts, and of the arteries. Many of them reach a high level of achievement, and, quite apart from the text, deserve the most careful study.

The second half is on radiotherapy and again opens with a discussion of the physical problems involved. Scattering and absorption are fully considered and the methods of dosimetry and of protection are clearly described. A description of radium and the special radiations it produces is followed by a full consideration of the effects of radiation of every kind upon the tissues, illustrated by photomicrographs of the cells in mutation. There follows a fully illustrated account of the application of radiation to various pathological conditions. The whole volume is spendidly produced and is evidently the outcome of most careful work and wide experience. It deserves close study by those who wish to master a field of increasing importance.

HENRY SOUTTAR.

ORTHOPAEDIC TEXTBOOK

Orthopaedic Surgery. By Walter Mercer, M.B., F.R.C.S.Ed., F.R.S.Ed. Fourth edition. Foreword by Sir John Fraser, Bart., K.C.V.O. (Pp. 1,016; 427 figures. £2 10s.) London: Edward Arnold. 1951.

The fourth edition of Professor Mercer's popular textbook runs to nearly a thousand pages, and for many candidates taking the higher examinations in surgery it is the orthopaedic Bible. In the new preface the author states that an attempt has been made everywhere to bring each section up to date, but it is a sad fact that he has by no means succeeded. For example, the prognosis of congenital dislocation of the hip is based on a report on "40 hip joints treated by manipulation at various ages from 1 year 7 months to 11 years" by Platt, whose personal series by the year of this edition had in fact exceeded 10 times that low number. In the section on arthroplasty all the materials once used as flaps for interposition, from muscle to pieces of pig's bladder, are again listed. For recurrent dislocation of the acromio-clavicular joint Watson-Jones suggests screwing the clavicle and the coracoid together; while several effete operations, such as Whitman's astragalectomy and Nicola's operation for recurrent dislocation of the shoulder, are described in full.

In the chapters on tuberculous infection the sedimentation rate is dismissed with a single brief mention, and the antibiotics receive none at all. On the subject of poliomyelitis, the numerical charting of muscle power is not described. In the treatment of paralysis of the arm, Clark's transplant of part of the pectoral muscle to replace the biceps, and the use of sublimis tendon to the ring finger in order to restore opposition of the thumb, are two tested procedures which well deserve a place.

For congenital forward bowing of the tibia the author permits straightening by osteoclasis or osteotomy; in the experience of others this leads almost inevitably to intractable non-union. For congenital pseudarthrosis the by-pass graft and its remarkable success in the hands of McFarland are not recorded. For recurrent lateral dislocation of the patella, medial transplantation of the tibial tubercle and patellar ligament is warmly recommended, though many surgeons have had to report anterior arrest of growth and posterior bowing of the tibia some years after this operation on children. Three pages and five operations for a deformity so uncommon as congenital absence of the radius are perhaps too many. Obviously there is room for further revision of this book.

K. I. NISSEN.

RESUSCITATION IN FRANCE

Anesthésie et Réanimation. By Dupuy de Frenelle and collaborators. Third edition. (Pp. 340; 66 figures; 1,200 francs.) Paris: Librairie Maloine. 1951.

This book on anaesthesia and resuscitation, edited by Dr. Dupuy de Frenelle and largely written by himself, is divided almost equally between accounts of pre- and post-operative care and anaesthetic techniques. Dr. de Frenelle's ideals are high: "Le but du réanimateur doit être que l'opéré sorte de la salle d'opération avec plus de vitalité qu'en y entrant," and he writes clearly and dogmatically in support of them. There are sections on the assessment of operative risk, pre-operative preparation, and the prevention and treatment of post-operative complications. Some of the pre-operative investigations he describes—such as Crampton's test and stimulation of the oculo-cardiac reflex—have been rejected or replaced by most British anaesthetists, and for the same reasons measures like direct blood transfusion and aerosol treatment for post-operative chest complications come strangely to the British reader. But no anaesthetist will quarrel with many of the points emphasized by italics or repetition—for example, that curare should not be used by the inexperienced anaesthetist or injected without apparatus for inflation at hand; that coughing must be encouraged as the first treatment of post-operative atelectasis; and the dangers of blood transfusion, which are too often ignored in operating-theatres in Britain. The section on anaesthetic techniques is sketchy; it gives accounts of thiopentone–curare and cyclopropane anaesthesia, but contains directions for using Ombredanne's inhaler, which still shows no sign of following its English counterpart from the anaesthetic-room to the instrument-maker's museum. There is nothing of great value in the book for British readers, but it reflects the interest in the care of the surgical patient that has been stimulated in France by the growing specialty of anaesthetics.

GORDON OSTLERE.

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HEART FAILURE

Research on heart failure has been intensified during the past few years since more accurate pressure-measuring devices have become available. Some of the recent work was discussed in London this week during the European Congress of Cardiology. The new knowledge gained has necessitated a revision of views previously held, and in his Oliver-Sharpey lectures, published in this and last week's *Journal*, Professor J. McMichael, who with his team at the Postgraduate Medical School has contributed much in this field, reviews the present position.

The concept of high and low output types of failure is still valid, but present emphasis is on pressure changes rather than on output alone. Heart failure can occur at any level of cardiac output, and the efficiency of the heart can be assessed only if the filling pressure of the ventricle and the work of the heart are known in addition to the output. An increased load on a ventricle may be sustained for many years by hypertrophy without any changes in filling pressure, and at this stage the heart responds to nervous and hormonal stimuli to increase its output as does the normal heart. In the early stage of overload the diastolic filling pressure of the hypertrophied ventricle is increased, but the ventricle contracts forcibly with a normal output and digitalis causes no obvious change in output or force of contraction.[1] This is the stage of what McMichael terms "compensatory" congestion, and the high filling pressure is maintained by a rise in auricular pressure. At a later stage the ventricular filling pressure rises further, but no corresponding increase in the work of the heart results. This he terms "hypodynamic" failure, and in this the ventricle responds to digitalis with increased force of contraction, better emptying, and a fall in filling pressure.

These changes have been studied largely in the right ventricle, but probably the left ventricle behaves in the same way. Owing to the low pulmonary arteriolar resistance the increased filling pressure of the left heart causes a rise in pulmonary arterial pressure and increased work for the right ventricle. This illustrates well the difficulty in interpreting the circulatory responses to drugs, since the left ventricle may be in hypodynamic failure and as a result the right will show compensatory congestion with increased venous pressure but without signs of right heart failure. In mitral stenosis the mechanical obstruction to blood flow at the mitral valve leads to changes in the pulmonary circulation very different from those found in left ventricular failure, although in each case dyspnoea is the dominant symptom. The resting pulmonary blood volume is often less than normal in mitral stenosis,[2] and on effort there may be little or no increase in cardiac output although the pulmonary artery pressure may be greatly raised by pulmonary arteriolar constriction. This constriction may protect the pulmonary capillaries against the high pulmonary arterial pressure, but only at the expense of increasing the load on the right ventricle.

The explanation of the action of digitalis is now rather less confusing to the clinician than it was a few years ago, when the experimental evidence seemed to indicate that in man its primary action was to reduce the venous filling pressure and that it had little direct action on the heart muscle. It has now been shown that one of the important actions of digitalis is to increase the efficiency of the failing ventricular muscle, a view long held by the physician and pharmacologist. The pressor effect of digitalis is less well known but may precede the beneficial action of the drug on the myocardium and thus occasionally cause acute left ventricular failure. The results obtained with digitalis in the treatment of heart failure due to mitral stenosis, particularly if the rhythm of the heart remains normal, are often less impressive than those seen in cases with left ventricular failure, and for this reason the success of the operation of mitral valvotomy in carefully selected cases is particularly welcome.

The reason why the hypertrophied ventricle fails is often obscure, and pathological examination of the heart muscle may provide no clue. The long-continued overload must sometimes be the answer, and in other cases there is an obvious precipating cause—such as infection, either rheumatic or intercurrent, impaired coronary blood flow, pulmonary infarction, paroxysmal tachycardia, or anaemia.[3] There remains a large group of cases where no cause for failure of the hypertrophied ventricle can be found, and in these biochemical changes in the myocardium may have reduced the cardiac reserve. Olson and Schwartz,[4] in their review of myocardial metabolism in congestive failure, distinguish two types of metabolic failure.

[1] Harvey, R. M., Ferrer, M. I., Cathcart, R. T., and Alexander, J. K., *Circulation*, 1951, **4**, 366.
[2] Kopelman, H., and Lee, G. de J., *Clin. Sci.*, 1951, **10**, 303.
[3] Sodeman, W. A., and Burch, G. E., *Amer. Heart J.*, 1938, **15**, 22.
[4] *Medicine (Baltimore)*, 1951, **30**, 21.
[5] Bing, R. J., *et al.*, *Circulation*, 1950, **2**, 513.
[6] *Science*, 1949, **110**, 411.
[7] Horváth, I., Király, C., and Szerb, J., *Nature, Lond.*, 1949, **164**, 792.

In the first there is a failure of energy production in the heart, as, for example, with inadequate oxygen supply or depletion of the co-enzyme thiamine (a deficiency which causes the heart failure of beriberi). In the second type energy production is normal, but there is a disturbance of energy utilization; this group includes cases of failure due to hypertensive and valvular heart disease. The cardiac efficiency and work are low in spite of a normal coronary blood flow and oxygen utilization, and the cardiac glucosides increase the efficiency of the heart without increasing its oxygen consumption, presumably through better energy utilization.[5] Szent-Györgyi[6] has shown that the ultimate contractile unit of heart muscle is the actomyosin fibril, a conjugate of the two muscle proteins myosin and polymerized actin. Polymerization of actin during diastole—the energy for this being derived from adenosine triphosphate, which is the sole immediate source of energy for muscular contraction—results in the formation of a long fibrous strand of actomyosin. Depolymerization, with shortening and spiralling of the fibril, causes muscular contraction and liberation of energy during systole. It has been shown that cardiac glucosides increase the shortening of the actomyosin fibril *in vitro*,[7] probably through improved utilization of available energy, and this may provide one explanation of the beneficial action of digitalis in some types of heart failure. Although with few exceptions the disease processes which cause heart failure are irreversible, normal heart function is often maintained for many years in spite of severe anatomical changes. The solution to the problem of why the heart eventually fails may well be found by research into the chemical changes which take place in the heart muscle.

NERVOUS CONTROL OF INTESTINAL MOVEMENTS

In his presidential address to the Physiology Section at the meeting of the British Association in Belfast this week, Professor R. C. Garry[1] began with a significant quotation from a paper written by Bayliss and Starling in 1899: "On no subject in physiology do we meet with so many discrepancies of fact and opinion as in that of the physiology of the intestinal movements." Professor Garry's subsequent review of the present stage of our knowledge in this field suggests that, in spite of a great deal of research carried out since 1899, our uncertainties are nearly as great to-day. When seeking the reason for this we must remember that we can attain full understanding of the mode of functioning of any given part of a complex organism only by an exact knowledge of its relations with the nervous system—its afferent and efferent fibres and the centres with which they make ultimate connexion. Thus it is usually taken as axiomatic that where both a sympathetic and a parasympathetic innervation to a viscus are present the one will be antagonistic to the other. In certain specialized regions of the alimentary canal this antagonism is unequivocal—for example, the parasympathetic fibres to the cardia and internal anal sphincter cause relaxation, while the sympathetic fibres cause constriction. Yet, in so far as the general motility of the gastro-intestinal tract is concerned, an antagonism between the two divisions of the autonomic system is a matter of debate. It is generally agreed that the sympathetic is inhibitory to the gut and motor to the sphincters, so that in periods of physical stress—when blood has been diverted from the viscera—gastro-intestinal activity is inhibited. Clinicians will be gratified to learn that Professor Garry finds that the most satisfactory grounds for this belief come from the surgeons, "who obtain the expected result in patients when they interrupt the sympathetic outflow on the hypothesis that it is inhibitor to the gut and motor to the sphincters." That the reverse results follow parasympathetic stimulation is not equally certain, according to Professor Garry. Thus no one has found a definite inhibitory outflow to the ileo-colic sphincter, and, when discussing gastric motility, McCrea and Macdonald[2] stated that the "theory of vagus nerve being excitor and splanchnic inhibitor is untenable." This view, however, has certainly not deterred every surgeon from the procedure of vagotomy as a treatment for peptic ulcer, but whether the disappointing results, recently assessed by Hansen,[3] are to be blamed on unsound physiology or on a too hopeful view of the aetiology of the condition remains to be seen.

The increased activity of the caecum and rectum after the taking of food into the stomach is so familiar an experience that few would question the fact, and its description as the "gastro-colic reflex" since 1904 gives it an almost prescriptive right to the title of a reflex. But the work of Douglas and Mann[4] cast some doubt on the correctness of describing the phenomenon as a reflex, though it failed to give a satisfactory explanation of the mechanism. Thus they showed that in dogs the increased ileal activity occurred when the vagi were cut, and they suggested that the "gastro-colic reflex" was no more than a rapidly propagated local response of the gut to distension, rather like the jogging wave which passes down a line of railway trucks during shunting. Now, presumably, we must describe the "reflex" noncommittally as a "post-prandial excitation of the intestine." Gregory's more recent work, however,

bears an opposite interpretation and tends to re-establish the phenomenon as a true reflex.[5]

The action of morphine on the intestine is of great interest to the clinician, especially in the treatment of paralytic ileus, and uncertainty about the physiology of the intestine is nowhere better illustrated than in the controversy whether a drug so universally observed to be constipating could increase the propulsive activity of the intestine. Recent studies by Williams and Streeten[6] seem to have clarified the matter; they found that morphine does indeed increase the activity of the gut, but in so far as this increased activity manifests itself as a contracture of the smooth muscle, locally obliterating the lumen of the gut, it delays the passage of the contents. These authors made a most useful study of the relative effects of a number of drugs on intestinal propulsive power, and by assessing their analgesic activities too they were able to show that amidone would have a 75 to 1 advantage over morphine as an analgesic in those conditions where a constipating action would be harmful. In a paper appearing elsewhere in this issue Dr. D. H. P. Streeten and Mr. J. N. Ward-McQuaid again refer briefly to this subject.

The sensory innervation of the gut provides more uncertainties, particularly about the nature of the receptors. In man the intestines may be burned, cut, or crushed without evoking a sensation, whereas distension gives rise to the characteristic "colic." The nature of a receptor that can fail to react to such noxious influences and yet respond to the relatively mild mechanical stimulus of distension poses an interesting problem for the physiologist. Presumably the receptors lie in the mucosa—at any rate those necessary to elicit the characteristic sensation in the colon that initiates the defaecation reflex.[7] Once again the surgeon will be gratified to learn that the operation of dorso-lumbar sympathectomy has provided useful information about the importance of the sympathetic afferent pathway in carrying sensory impulses from the intestine to the central nervous system.[8]

These are a few of our uncertainties; and the reasons for them are not far to seek. The principal cause resides in the extraordinary complexity of the peripheral nervous pathways, interrupted as they are by the plexuses of Meissner and Auerbach, the functions of which are by no means completely understood. If to this be added the fact that the mode of activation, and the potentialities for spontaneous activity, of the smooth muscle of the gastro-intestinal tract are still matters of dispute, there is obviously still a long way to go before a certain knowledge of the factors governing the motility of the system can be attained.

While the remark of Bayliss and Starling, quoted earlier, undoubtedly applies with some cogency to-day, the outlook is fairly promising. Thus comparatively recent neurophysiological studies on the functions of the orbito-frontal cortex are providing a sound basis for an understanding of the relationship of the higher centres to the viscera—a matter of great interest to those whose leanings are towards psychosomatic medicine. For example, Babkin[9] recently described the inhibitory effects of stimulating the cingulate gyrus on the motility of the pyloric end of the stomach; according to him this region of the cortex exerts an inhibitory effect on the activity of the hypothalamus, which itself reacts on a medullary centre controlling gastric activity. Thus two regions of the brain that seem to be especially involved in determining "patterns of emotional reactions" are also involved in gastric motility. Again, recent developments in pharmacology are providing the experimental physiologist with a variety of new drugs capable of blocking nervous activity at different levels of the peripheral pathway. With the aid of these it may be possible within a few years to unravel the complexities of the myenteric plexuses and lay bare the potentialities of the smooth muscle for spontaneous activity.

[1] *Advancement of Science*, 1952, No. 34 (in the press).
[2] *Quart. J. exp. Physiol.*, 1928-9, **18**, 161.
[3] *J. Int. Coll. Surg.*, 1950, **14**, 577.
[4] *Amer. J. dig. Dis.*, 1939, **6**, 434; 1940, **7**, 53.
[5] *J. Physiol. (Lond.)*, 1950, **111**, 119.
[6] *Brit. J. Pharmacol.*, 1950, **5**, 584.
[7] Goligher, J. C., *Ann. roy. Coll. Surg. Engl.*, 1951, **8**, 421.
[8] Bingham, J. R., Ingelfinger, F. J., and Smithwick, R. H., *Gastroenterology*, 1950, **15**, 18.
[9] *Edinb. med. J.*, 1950, **57**, 419.

COELIAC DISEASE

Little has been added to the clinical picture of coeliac disease since it was first described by Samuel Gee[1] in 1888, but many investigations into aetiology and treatment have been undertaken. They have resulted in the differentiation of coeliac disease from other diseases comprising the coeliac syndrome, in the elaboration of the partition theory of fat absorption, and in the discovery of the effect of starch on fat absorption. It has become fashionable, though at times confusing, to use the term "coeliac syndrome" to describe illnesses characterized by steatorrhoea, malnutrition, and abdominal distension, but as a result of the work of Dorothy Andersen[2] and others pancreatic fibrosis has become a separate entity. The three main clinical types of pancreatic fibrosis are now well recognized; the associated histological changes have been described, and it is often possible to distinguish clinically between pancreatic fibrosis and coeliac disease.

The investigations of Frazer and his colleagues[3 4] into certain aspects of fat metabolism have led to the development of the partition theory of fat absorption and to new methods of investigating patients suffering from coeliac disease. This hypothesis suggests that small particles of unsplit fat about 0.5 μ in diameter are absorbed into the lacteals, while fatty acids pass into the portal circulation. The technique of counting these small fat particles (chylomicron count) has been developed, while the fallacy of estimating the fat content of isolated specimens of faeces has also been exposed and the more reliable fat-balance test substituted.

Since Samuel Gee stated that "if the patient can be cured at all it must be by means of diet" the main treatment for coeliac disease has been dietetic. Gibbons[5] in 1889 prescribed cream and fresh butter, and maintained that starchy foods were injurious. Howland[6] also regarded failure to digest carbohydrate as the primary trouble and pointed out in 1921 that coeliac disease usually arose when starch was first added to the infant's diet. Haas[7] favoured a diet containing over-ripe bananas, because during ripening the starch in this fruit is converted into sucrose. In 1935 Birchner-Benner[8] advocated a diet mostly of fruit and vegetables, and a similar diet has been used by Wyllie and his colleagues.[9] Many workers, however, have believed that the basic fault in coeliac disease is failure of fat absorption and have recommended a diet low in fat and high in protein; but recent investigations have shown more clearly the part played by both starch and fat on the progress of this disease. Sheldon[10] found, as a result of fat-balance studies in 15 children with coeliac disease, that withdrawal of starch led to an increase of 15% in fat absorption, and that these children could tolerate fat in normal quantities when on a low-starch diet. A similar relation exists between the amount of dextrin in the diet and fat absorption.[11] It was also shown by chylomicron curves that particulate fat absorption was deficient in coeliac disease but that absorption increased as the disease became less severe.

A paper by Dr. Charlotte Anderson and her colleagues[12] is an admirable exposition of the concept of gastro-intestinal function in coeliac disease and of the effect of dietary wheat flour on the course of this condition. The study is based upon the clinical, biochemical, and radiological findings in 10 children aged 9 months to 6 years. The clinical features were those generally accepted for a diagnosis of coeliac disease, and investigations showed an increased amount of faecal fat, normal pancreatic enzymes, delayed and depressed chylomicron counts, flattened glucose-tolerance curves, and abnormal radiographic patterns in the small intestine. When corn flour or soya flour was substituted for wheat flour present in the normal hospital diet the clinical condition of these children improved greatly, an improvement reflected in the biochemical and radiological findings. Reintroduction of the original diet led to a recurrence of symptoms. Furthermore it was found that wheat gluten and not wheat starch itself was responsible for the deterioration. These studies show that the diet of a child suffering from coeliac disease may be full and varied provided that wheat and rye flour are avoided and replaced by corn flour and soya flour. Details of a suitable diet are given elsewhere in this issue (p. 624).

1 *St. Bart's Hosp. Rep.*, 1888, **24**, 17.
2 *Amer. J. Dis. Child.*, 1938, **56**, 344.
3 *J. Physiol. Lond.*, 1943, **102**, 306.
4 *British Medical Journal*, 1947, **2**, 641.
5 *Edinb. med. J.*, 1889, **35**, 321.
6 *Trans. Amer. pediat. Soc.*, 1921, **33**, 11.
7 *Amer. J. Dis. Child.*, 1924, **28**, 421.
8 *Kinderernährung*, Zurich, 1935.
9 *Arch. Dis. Childh.*, 1951, **26**, 4.
10 Ibid., 1949, **24**, 81.
11 Sheldon, W., and MacMahon, A., ibid., 1949, **24**, 245.
12 *Lancet*, 1952, **1**, 836.

DIAGNOSIS OF CANCER FROM ISOLATED CELLS

Although there is no single morphological feature or staining reaction by which a malignant cell can be positively identified, cancer cells do show abnormalities which, in a known context, betray their origin to a trained observer. Cases of malignant disease diagnosed by smears of body fluids and secretions have been reported by hundreds of authors over the past 80 years, but most pathologists have felt the method to be unreliable.

Two staining methods have been principally used. First, smears can be rapidly dried in air, fixed in alcohol, and stained by one of the Romanowsky stains exactly as for blood films; this method is applicable only to material which will dry instantaneously in air. Secondly, smears may be fixed while still wet (usually in alcohol–ether mixture), and stained with haematoxylin and eosin or with Papanicolaou's stains, which are designed to show degrees of cornification in squamous cells. This method is the best for vaginal smears and sputum. Smears have to be searched methodically, as only occasional cancer cells may be found among thousands of normal ones; the examination of one film may take 10 minutes or more.

Nine years have passed since the publication of Papanicolaou's monograph[1] on the smear diagnosis of uterine carcinoma, and his technique is now widely used in America. Time has already shown its value and limitations. The cervix uteri is an accessible organ, and the Papanicolaou method is not a substitute for biopsy in cases where carcinoma is suspected. But it is a simpler, quicker, and cheaper method for the routine survey of large numbers, and vaginal or cervical smears

are now used mainly for the "screening" of gynaecological out-patients, or of supposedly healthy women in American cancer detection clinics. It has also been introduced in several British centres.[2] The emphasis in screening is on maximum sensitivity, even at the cost of some false positive reports. In the recent series of Haynes and his colleagues[3] 6,816 persons were examined, mostly gynaecological patients, and after excluding clinically recognizable cases 36 (0.53%) were discovered to have uterine carcinoma; without a smear they would have "passed without suspicion through the office of the most competent gynaecologist." There were 18 false positive results—i.e., 7% of all positives. Provided that a positive report is taken only as an indication for biopsy, it does no harm; the false positive rate in this series is lower than in most large series.[4-6] Other authors have found a similar percentage of subclinical growths among gynaecological out-patients,[7] but among normal women the figure has been put as low as 0.12% of 16,246 cases.[8] Many of the cases found are of carcinoma *in situ*, the natural history of which is not fully known. Endometrial carcinoma is more difficult to detect than cervical carcinoma and accounts for most of the published false negatives.

Carcinoma of the lung is not always accessible to biopsy, and a cytological report on sputum or bronchial aspirations may be the only positive evidence. This is not a screening test, and reliability is essential. In expert hands false positives can be practically eliminated. Dudgeon and Wrigley[9] detected 68% of 38 pulmonary (and laryngeal) growths by sputum examination; Wandall's figure[10] was 84% of 100 cases; and Herbut and Clerf,[11] using bronchoscopic aspirations, have detected 88.8% of 285 cases of bronchial carcinoma.

Smear methods are found useful for the rapid diagnosis of cerebral tumours exposed at operation.[12] Applied to urine, prostatic secretions, and gastric washings, the method has been found difficult and not very useful clinically. Tumour cells can be identified in over 50% of cases of malignant pleurisy and ascites, and this examination is a long-established one. In the United States serous fluids are often examined by Papanicolaou's method as well as by sections of centrifuged sediment; neither of these methods represents an advance on rapid air-dried Romanowsky-stained films—a technique which is also the standard method for detecting tumour cells in cerebrospinal fluid and in bone marrow.

In sum, the search for malignant cells is no more laborious nor less valuable than many other diagnostic procedures; but those undertaking it must remember that a biopsy is the only final proof of cancer.

1 Papanicolaou, G. N., and Traut, H. F., *Diagnosis of Uterine Cancer by the Vaginal Smear*. 1943. New York, Commonwealth Fund.
2 *Proc. roy. Soc. Med.*, 1951, **44**, 305.
3 *J. Amer. med. Ass.*, 1952, **148**, 457.
4 Fremont-Smith, M., Graham, R. M., and Meigs, J. V., *New Engl. J. Med.*, 1948, **238**, 179.
5 Burns, E. L., Hartung, W. H., and Brittingham, E., *Arch. Path., Chicago*, 1950, **50**, 699.
6 Nieburgs, H. E., and Pund, E. R., *J. Amer. med. Ass.*, 1950, **142**, 221.
7 Reicher, N. B., Massey, B. W., and Bechtold, E., *Amer. J. Obstet. Gynec.*, 1950, **59**, 860.
8 Emerson Day, American Cancer Society Symposium, October 23, 1951.
9 *J. Laryng.*, 1935, **50**, 752.
10 *Acta chir. scand.*, 1944, Supp. 93.
11 *Amer. Rev. Tuberc.*, 1950, **61**, 60.
12 Dorothy Russell, *Recent Advances in Clinical Pathology*, 1951, 2nd ed., p. 455, London.

FOOT-AND-MOUTH DISEASE

Foot-and-mouth disease has been in the headlines of the daily press now for nearly a year. The country has been disturbed to see the losses in food and money mount despite vigorous action by the Ministry of Agriculture, and questions have been asked, in Parliament and elsewhere, about the slaughter policy for controlling the disease and about the research being undertaken on this most infectious of all animal diseases. A committee has been appointed to inquire into the methods used for controlling outbreaks of the disease. At the request of the Agricultural Improvement Council for England and Wales the Agricultural Research Council has prepared an interim report[1] on the research being done by the Foot-and-Mouth Disease Research Institute at Pirbright. This 12-page booklet provides a succinct statement in popular language and is intended to enable all those interested in the disease to understand the nature and complexities of the problems presented.

It is to Continental scientists that we owe the early discoveries that the infectious agent is a virus, that it may exist in one of several different immunological types, and that protection for a limited period against homologous strains can be provided by a killed virus vaccine. In this connexion it has just been announced from Paris that workers at the Government veterinary research station at Alfort have discovered a greatly improved method of culturing the virus for vaccine production.[2] The main contributions of the Pirbright team have arisen from their policy of using quantitative methods—for example, to determine the degree of protection afforded by vaccines prepared from various strains against the same or other strains. Work of this nature is only possible in a country where cattle are available that are known with certainty never to have had contact with the disease, nor to have been vaccinated. However, doing such work in a country normally free of the disease necessitates elaborate precautions to prevent escape of the virus from the experimental station. This requirement makes the work costly and slow.

The quantitative work at Pirbright has brought to light differences between strains not previously known. For instance, some strains show a predilection for a particular species of livestock. Another difference detected is that strains of the same type may show minor but important immunological variations. The analogy with influenza in this respect is noteworthy. The Pirbright workers have developed a complement-fixation test which has proved of great value in making rapid diagnosis and in studying relationships between strains of foot-and-mouth virus. As a result the Institute has become recognized, as yet unofficially, as a world centre for typing strains.

One of the Pirbright team recently discovered that unweaned mice are susceptible to the virus. With most strains, unweaned mice are as sensitive as cattle in detecting small amounts of virus or antibody. They also provide good yields of virus. In all these respects they are distinctly superior to the only other susceptible laboratory animal, the guinea-pig. One of the limiting factors

1 *Foot and Mouth Disease Research*, 1952, H.M.S.O., London. Price 6d.
2 *Manchester Guardian*, September 4.

in experimentation with the virus of foot-and-mouth disease is that cattle have been necessary for many of the tests. The use of unweaned mice should help to speed up the work.

Biophysical investigations on the virus have shown that, as with so many other viruses, there are two components—one 20 mμ in diameter which is infective and gives a reaction in the complement-fixation test, the other 6.5 mμ in diameter which is non-infective but also reacts in the complement-fixation test.

This report should assure those alarmed about the present epidemic that British veterinarians are not only enlightened in their policy on foot-and-mouth disease but that they are well to the fore in research on all aspects of the disease. Further reassurance is to be found in the statement that a large expansion of the institute at Pirbright is planned. This should allow a speeding up as well as an extension of the scope of investigations on foot-and-mouth disease.

TREATMENT OF INTERMITTENT CLAUDICATION

The assessment of the value of various methods of treatment of diseases which may undergo spontaneous improvement is always difficult. This is especially true of a condition such as intermittent claudication, where assessment often depends on the patient's own evidence. Drs. M. Hamilton and G. M. Wilson[1] have devised an objective test of improvement. A group of patients were made to carry out a set exercise of walking over a pair of steps 18 in. (45.7 cm.) high, the number of circuits made before pain developed being noted. There was a considerable fluctuation in exercise tolerance over a period of weeks, in the absence of any treatment, in a group of 10 patients. Furthermore, one patient was given inert tablets for several weeks, and during this time there was a progressive improvement in his tolerance to exercise. The drugs tested were vitamin E, "priscol," methyl testosterone, nicotinic acid, dihydroergotamine, papaverine, and aminophylline. Improvement was noted in one patient out of 11 who received vitamin E, and in one patient out of 10 who received testosterone. None of the other drugs appeared to improve the exercise tolerance. As the authors comment, this is perhaps not surprising, as during exercise the blood vessels are already under the influence of powerful vasodilators, the tissue metabolites. Sixteen patients were treated with intermittent venous occlusion, but only two showed significant improvement: the authors considered that this improvement was more likely to be due to the rest in bed than to the treatment, and to support this contention they gave treatment to one leg of each of two patients who had symptoms in both calves; in both patients the improvement was shared equally by both legs.

These experiences with vitamin E contrast with those of Boyd, Ratcliffe, Jepson, and James,[2] who used the drug in 81 patients and found considerable improvement in 64; they suggested that it should be given for four to six weeks before improvement could be expected. They measured the patients' walking distance with an instrument called a claudicometer, which consisted of a motor-driven endless belt on which the patient had to walk, although it is not clear from their paper whether this apparatus was used to assess every patient.

Lumbar ganglionectomy is also used as a treatment of intermittent claudication and is the subject of controversy. Telford and Simmons[3] found that all their patients were helped by sympathectomy, but that the majority could walk no more than an additional 50 to 100 yards (91.5 metres) before the onset of pain. Boyd and his colleagues, on the other hand, report very good results from sympathectomy for the type of claudication in which the pain remains at a steady level: they obtained poor results in patients who were forced to stop by an increasingly severe pain. For those who suffer from this severe type of claudication in the calf, and whose skin nutrition is adequate, section of the tendo Achillis offers most prospect of relief, although it is disappointing in some patients, who limp later from pain in the foot or thigh.

In these studies the results of treatment were not correlated with the levels of arterial block, although Telford and Simmons did state that the results of sympathectomy were better when the block was proximal. Most cases of claudication in the calf are due to narrowing or thrombosis of the femoral or popliteal artery, and less commonly to disease in the muscular vessels. Occasionally it is due to disease above the inguinal ligament, as a recent paper by Professor A. Kekwick and Drs. L. McDonald and R. L. Semple[4] shows. These authors found in a series of 53 cases of intermittent claudication that eight were due to high blocks—seven in the iliac vessels and one in the aorta. They describe the clinical findings in this type of case and lay stress on the extension of the pain to the thigh, the weakness, delay, or absence of the femoral pulse, wasting of the affected thigh, and wasting or hypotonia of the buttock. The low incidence of pain in the buttock, absent even in the patient with an aortic block, is remarkable. The diagnosis can be confirmed instrumentally by the disappearance of the pulsations from the thigh after exercise (the authors used a tonoscillograph) or by aortography.

For those with a short history suggestive of a recent arterial thrombosis a month's bed rest, with reflex vasodilatation to promote the collateral circulation, will improve the symptoms in many cases; vitamin E can be given during this time in a dose of 400 mg. a day. A number of these patients will continue to improve. Subsequent treatment will depend on the severity of the symptoms in relation to the distance the patient needs to walk. When the pain on walking remains at a steady level of intensity a lumbar ganglionectomy will lengthen the walking distance to a useful degree in a large proportion of patients. For the severer cases of claudication in the calf sympathectomy is disappointing, and a section of the tendo Achillis, preceded by sympathectomy when the skin nutrition is doubtful, offers the best prospect of relief. The number of patients who eventually lose the limb is small.

1 *Quart. J. Med.*, 1952, **21**, 169.
2 *J. Bone Jt Surg.*, 1949, **31B**, 325.
3 *British Medical Journal*, 1946, **1**, 386.
4 *Quart. J. Med.*, 1952, **21**, 185.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

NEPHRITIS—I. AETIOLOGY, COURSE, AND DIAGNOSIS

BY

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The Course of Nephritis

It is impossible to think at all clearly on the subject of nephritis without first knowing something of the natural history or course of the disease, and it is upon this that the present classification of nephritis depends.

All clinicians recognize a condition termed "acute nephritis" which usually follows a sore throat and starts suddenly with the three cardinal features of oedema, haematuria, and hypertension. It is in the more chronic phases that we get into difficulties. Some would divide what they call glomerulonephritis into the acute, subacute, and chronic stages, adding another disorder called "nephrosis," which is clinically subacute nephritis without hypertension. The disadvantages of such a classification are twofold. (1) It suggests a course which most cases do not follow at all, for the majority of cases of subacute nephritis have never passed through an acute phase, and many cases of acute nephritis progress slowly to the chronic terminal stage without any interval which could possibly be called subacute. (2) Neither clinicians nor pathologists can agree on what is nephrosis and what is nephritis.

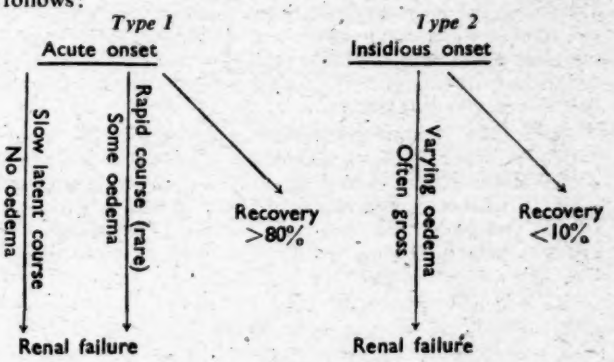
A. W. M. Ellis, from a study of the natural history of the disease combined with careful histological examination, prefers to divide nephritis into two types, separable on both clinical and pathological grounds, which he simply calls Type 1 and Type 2.

Although there are occasional difficulties and we shall not reach any kind of finality until the aetiology of nephritis is better understood, I have found the Ellis classification to be by far the most satisfactory from a practical point of view and will use it in these articles.

Type 1 nephritis starts with an acute attack. As it generally follows, by an interval of from one to three weeks, a streptococcal tonsillitis, it occurs most often in children and young adults. More than 80% of cases of acute Type 1 nephritis recover completely. Of the remainder, a few die in the acute stage, a few run a rapidly downhill course with persistent or recurrent oedema, and the remainder become latent for many years and eventually develop renal failure with hypertension. During the latent phase albuminuria persists, but not oedema; the patient returns to work and feels well, but careful examination reveals a deteriorating renal function and a rising blood pressure. Eventually—usually after about five to fifteen years—he develops symptoms from uraemia (renal failure), hypertension, or both, and enters the terminal phase of his illness.

Type 2 nephritis, on the other hand, starts insidiously with a complaint of oedema, usually of the legs. It is not commonly preceded by infection and may affect persons of any age, including infants. It is characterized by gross persistent or recurrent oedema and gross albuminuria without macroscopic haematuria. The blood pressure may remain normal for months or years (corresponding to nephrosis of other authors) or may be raised from the beginning. The recovery rate is low, but probably more than the 5% which Ellis quotes. The remainder may die of intercurrent infections (although this is a much less common termination than it was before antibiotic therapy) or slowly pass into a state of hypertension and renal failure. In this last stage the oedema may disappear.

The course of nephritis may therefore be illustrated as follows:



Pathology

Pathology need not concern us closely, but in most cases it is possible at all stages of the disease to distinguish between Type 1 and Type 2 nephritis histologically. In the former the glomerular lesion in the acute stage is obvious and very cellular; this leads on to crescent formation and glomerular fibrosis, with complete disappearance of many glomeruli by the time the chronic stage is reached. The glomerular lesion of Type 2 is an insidious hyalinization. Glomeruli are preserved even though they be non-functioning. There is much less cellularity and less fibrosis, and therefore less contraction of the kidney. Tubular changes in the early stages are more in evidence.

Aetiology

Type 1 nephritis is one of those diseases which seem to consist in an abnormal response of tissues to infection. It is therefore related to allergic disorders and to conditions such as acute rheumatism, which it sometimes accompanies, and to rheumatic or anaphylactic purpura (Henoch-Schönlein syndrome), which it may complicate. In some cases it is hard to draw a dividing line between acute nephritis and polyarteritis nodosa, and when we know more about this group of diseases perhaps we shall think it unnecessary to make these arbitrary clinical distinctions except for convenience of description.

Experimentally, acute nephritis can be produced by giving "anti-kidney" serum; when an animal is immunized with an emulsion of kidney of another species its serum develops antibodies to that type of kidney. When this animal's serum is inoculated into an animal of the species from which the kidney emulsion was obtained it produces clinical and histological nephritis. These experiments were carried out originally by M. Masugi in 1933, but have often been repeated. Other workers have produced nephritis in rabbits and rats by an injection of homologous—that is, rabbit or rat—kidney suspension plus streptococci. Thus it seems possible that in human acute nephritis an antigen is formed by the action of streptococcal toxin upon the patient's kidneys. The patient (after the usual interval for immunization) then develops an antibody to this antigen which acts on the kidney, producing nephritis.

The aetiology of most cases of Type 2 nephritis is completely unknown. It is not, of course, certain that it has a different aetiology from Type 1, but there is a good deal to suggest that it is separate and distinct. It is most interesting that "nephrosis" has recently been reported in children who

have been given calomel in the form of teething powders. The connexion has not been finally proved, but in some cases the renal symptoms entirely cleared on withdrawal of calomel and returned when its administration was recommenced. Others have recorded similar cases occurring during troxidone therapy for petit mal.

Diagnosis

In the acute stage the diagnosis of Type 1 nephritis usually presents no difficulty, but in a few cases the symptoms are predominantly those of acute heart failure. Whether this is due to the acute hypertension which accompanies the illness or, more probably, to haemodilution as a result of retention of water and salt is not entirely established. Sometimes the signs and symptoms of the acute stage are minimal and may pass unnoticed. Sometimes convulsions are the first evidence of disease.

Acute focal nephritis is looked upon by some as a subvariety of acute nephritis. Typically it is seen at the height of an infection, and manifests itself solely by haematuria without oedema or hypertension. Its prognosis is good, but it may return if the infection recurs. It is much less common now that most pyogenic infections are promptly treated by sulphonamides or penicillin.

The oedematous stage of Type 2 nephritis is indistinguishable on ordinary clinical examination from two other disorders which cause the same syndrome—namely, the diabetic glomerulosclerosis which occurs as a (very deadly) complication in some diabetics of long standing, and amyloid disease affecting the kidney. In the first the history of preceding diabetes gives the clue; in the second the history of chronic purulent or tuberculous infection. The correct diagnosis of amyloid disease is very important nowadays, and may often be confirmed by the congo red test (the injected dye disappears very rapidly from the blood serum as it is taken up by the amyloid material). I have seen several cases of amyloid disease with gross albuminuria and renal oedema recover completely when an efficient attack on the underlying infection was made by surgery and antibiotics.

The finding of a symptomless albuminuria at a routine examination may raise a diagnostic problem which cannot here be dealt with fully. Tests for orthostatic albuminuria, tests of renal function, radiology, and cystoscopy may all have to be employed. Patients in the latent stage of Type 1 nephritis often feel perfectly well and may come into this group, the albuminuria being found by an examination for military service or for life assurance. There should be a history of an acute attack of nephritis in the past, and renal-function tests (concentration power and urea clearance) will show impaired efficiency. The blood pressure will be raised.

Chronic non-oedematous renal disease, leading to renal failure, presents two kinds of diagnostic difficulty. The first is the difficulty of realizing that the patient has renal failure. The reserves of the kidney are such that patients with slowly progressive renal disease do not complain of symptoms until renal failure is in a very advanced stage. If it is accompanied (as is often the case) by hypertension it is usually the hypertensive complications, such as headache, retinopathy, or cardiac failure, which bring the patient to the doctor. It may then be difficult to know whether the hypertension or the renal disorder is primary. I have dealt with the relation of hypertension to renal disease in a previous article of this series (*British Medical Journal*, 1950, **1**, 951). Patients with renal failure who have no severe hypertension most often complain of the symptoms of anaemia—languor, pallor, dyspnoea, and palpitation—for a normochromic anaemia, unresponsive either to iron or to liver, invariably develops as the blood urea rises. Others make no complaint until advanced uraemia brings with it anorexia, vomiting, loss of weight, and extreme weakness. Uraemia should be suspected if such a patient has a dirty pallor like fading sunburn, if he complains of thirst and nocturia, and if his skin is dry. In my opinion uraemia has no characteristic smell, but a dry dirty mouth with bleeding gums (which are common in the terminal stage) provide what has been mistaken for it.

Practically all cases of renal failure (uraemia) have albuminuria, and all have a raised blood urea, so it is not difficult to prove the diagnosis once suspected. When renal failure has been diagnosed the problem is to determine its cause, and this is important, for a few cases are amenable to treatment. Dr. D. A. K. Black has dealt with the subject of uraemia in his article in this series (*British Medical Journal*, 1950, **1**, 893), but some points in diagnosis must be restated.

Uraemia may occur as the end stage of any progressive renal disease, including the various types of nephritis which are the subject of these articles. The commonest causes are nephritis, chronic pyelonephritis, and the malignant phase of essential hypertension. Of these, chronic pyelonephritis requires emphasis particularly as an important cause of renal failure. A history of acute "cystitis" or "pyelitis" in the past normally provides the clue. In the chronic stage the urine may no longer show evidence of active infection. When uraemia terminates Type 1 or Type 2 nephritis there should be a past history of an oedematous phase, which may have occurred many years before.

Extrarenal uraemia may occur in salt deficiency and in alkalosis and is especially important in diagnosis, as it is curable.

It is a fair rule that in the young the commonest causes of renal failure are nephritis and chronic pyelonephritis. In the middle-aged malignant hypertension is added to these two. In the elderly the diagnosis of uraemia is usually wrong, except in association with prostatic disease. Most elderly patients suspected of uraemia have cerebral arteriosclerosis with thrombosis. A few, however, are genuine, usually from chronic pyelonephritis or multiple myelomatosis.

Hypercalcaemia must not be forgotten in the differential diagnosis of renal failure. It may occur in hyperparathyroidism, or as the result of taking calciferol in high dosage, and is curable if not too advanced. There are, of course, many other causes of renal failure, including congenital and so-called surgical renal disorders.

[*Part II, which will appear in our next issue, will deal with the prognosis and treatment of nephritis.*]

Correction.—In the Refresher Course article on "Rheumatic Fever" (July 19, p. 142) vitamin K is recommended for the treatment of haemorrhagic complications of salicylate therapy. The preparation suggested is Inj. menaphthon., 20 mg., but it should be given intramuscularly, *not* intravenously as stated in the article. Inj. menaphthon. is an oily solution and therefore unsuitable for intravenous injection.

SHIP SURGEON

[FROM A SPECIAL CORRESPONDENT]

Going to sea, like playing golf, is a pastime most doctors find time for only at the two extremities of their professional lifetime. There are a handful of practitioners who have made the Merchant Service their career, but these are hard-worked men on big P. & O.s and Cunarders with a couple of thousand people under their care, two or three ship's hospitals, an operating theatre, and even an *x*-ray apparatus. My life illustrates the more usual existence of a ship surgeon: I go to sea for a holiday, which I am taking at present as the only doctor on a small passenger steamer outward bound for Australia.

The medical centre of my ship is next to my cabin, at the after end of the promenade deck. There is a small hospital with four bunks in it, a bathroom, and a combined consulting-room and dispensary next door. At nine in the morning I hold surgery for the crew, with the assistance of my hospital attendant. He is a capital fellow, whose accomplishments include the ability to tie a perfect figure-of-eight bandage, play the saxophone, and perform card tricks, all of which he demonstrates to me frequently. He has an efficient way of organizing the untidy line of men who collect

in the alley-way waiting for the surgery door to open. "Now then," he commands. "Black draughts first, coughs next, oddments afterwards, and doses last."

The cases are not exciting clinically. There are cuts, bruises, and sprains; burns from the engine-room; sore throats and colds; and gonorrhoea comes after every stop in port as surely as the wake follows the ship.

Treatment is entered in the surgeon's log book against the man's name and rating. This soon gives one a picture of the different functionaries required to run a ship. Every vessel is a floating village: apart from the deck and engine-room staff, there is the butcher, the baker, and the lamp trimmer; the carpenter, the electrician, and the barber; and all of us are under the unanswerable jurisdiction of the Squire living below the bridge. It is essential to show a proper appreciation of the different grades of seniority—as between a fireman and his immediate inferior, a trimmer, for instance. On my first day at sea a fireman came up to the surgery with a gash in his arm. He was one of the old type with forty years' sea time to his credit who wore the buckle of his belt at the back—a relic from the days of coal furnaces which heated the metal almost red in its usual position. "Fireman or trimmer?" I asked him absently. He was horrified. "Trimmer!" he shouted, pointing to his wound. "Trimmer, doc.! D'you think a trimmer would have blood like that?"

Fiat Mistura

One of the first difficulties I encountered at sea was dispensing. It is all very well to write a mental prescription for mist. expect., but it is a forbidding task to transform the thought into a bottle of medicine. Under Board of Trade regulations the ship is obliged to carry a large stock of drugs ranging from amylum (what on earth could one do with amylum?) to tinct. zingiberis mitis. The heavy square bottles stand in discouraging rows, all labelled in Latin. I had certainly attended a course of lectures in materia medica, but as these were always held on Saturday mornings in my medical school I usually left quietly after the board was passed round for the students' signatures. Fortunately, my predecessor apparently had his classes on Saturdays too, and several of the bottles bore helpful labels on their bases giving such experimental data as "Seems good for diarrhoea"; "Try for coughs"; or "Apparently inert."

I limit my therapy to simple mixtures. Once I gave way to ambition, when the captain himself sent his steward down for a bottle of "stomach mixture." The rows of possible ingredients and the occasion fired me like a French chef preparing a banquet. Unfortunately I mistook the calamine powder for the pulv. rhei co. and produced an aromatic sort of putty, which we were later able to use up for minor irritations on the crew's feet.

The half-hour after the crew's surgery is allotted to the passengers. Apart from the usual small troubles, about half their number provide cases of seasickness in the first few days after leaving port. I believe all except the experienced travellers come on board expecting to vomit, and most of them have their personal empirical remedies against it. Some of them hurry to lie down, others insist in remaining up; as many think they should eat a good meal as believe any sort of food to be disastrous; a few tie a scarf over one eye, or tightly round their neck; and the majority make for the bar as soon as it opens to test the prophylactic quality of a large (duty-free) brandy. I don't think any of these remedies have any value whatsoever.

After surgery the stewardess and I visit passengers sick in their cabins, and I take my daily list of crew off duty to the captain—an excellent opportunity to discover in what sort of temper the old gentleman happens to be for the day. (The captain's daily mood is a matter of importance in a ship unbelievable to a landsman.) Then I go forward to the main hall for the daily inspection of the ship.

Inspection is carried out by the captain, the chief engineer, the chief officer, the purser, and myself. We nose our way through the passenger and crew accommodation, trying to look as unpleasant as possible, and file with dignity in and out of the lavatories. From these inspections I soon learnt that ships have a detailed anatomy of their own that must be grasped rapidly to understand what your shipmates are talking about.

Sports and Pastimes

Mr. P. G. Wodehouse maintained that the ship's doctor could always be located, in cases of emergency, playing deck quoits with the prettiest girl on board. This is not entirely true, for the prettiest invariably becomes the protégée of the chief officer, and the doctor is obliged to partner her best friend. My morning's work is over by eleven-thirty, which leaves an hour before lunch for gentle exercise with a rope quoit in the sun. This is all part of the job. According to the company's book of instructions for its surgeons the doctor is required to play a leading part in the social life of the ship—and a more agreeable means of earning a living I think has yet to be discovered.

After lunch everyone on board not immediately concerned with the running of the ship turns into his bunk or dozes in the sun. This is a well-established maritime habit that I found no reason to break. I hold a second surgery in the evening, which is identical with the first.

The low prices of drinks and cigarettes and the abundant service make entertainment easy for everyone on board. There is usually a cocktail party before dinner that the doctor is expected to attend—and he often comes up to expectations. At dinner the doctor, as a senior officer, has his own table in the saloon—an arrangement that I have found to be one of the small snags in an otherwise delightful existence. My shore colleague has to work far harder, but at least he does not have to eat with his patients—or, worse still, their mothers and fathers. Passengers have a distressing inclination to carry a discussion of their own and their companions' ailments outside the consulting-room. Otherwise their conversation is safely predictable—the favourites for the shuffleboard tournament; whether there is anything "on" between the tall young man in the blazer and that red-headed girl; if the ship is rolling a little more or a little less to-day; should the captain be told of that peculiar object which floated past in the afternoon; and, in bad weather, the frank possibility of the ship going down in the night with all hands.

The Other Half

In the evening there are the usual shipboard dances and mild gambling games that vary no more from ship to ship than the shape of the funnels. I prefer to sit talking to one or other of the officers off watch: the seafarer's life is such an extraordinary one it is worth taking the trouble to understand it. They speak of the world with the familiarity of a man describing his suburb, and an ocean crossing to them is no more than a bus ride. They are constantly fighting against the wind, the weather, and unsignposted space, which their countrymen ashore gave up doing in person many centuries ago. Their mixing with an unceasing succession of people from all races and all shades of character gives them a sharp sense of values, yet they are alarmingly ingenuous over their own affairs. All sailors wonder why they went to sea, yet they feel uncomfortable away from it. They are companionable, light-hearted, and often superstitious: there's a streak of the gipsy in all of them.

Medical and surgical emergencies are always likely to disrupt the otherwise placid life of a ship's doctor. At such times your responsibilities suddenly become greater than your shore colleague's, for there is no specialist's opinion to turn to, and however well the ship is equipped some improvisation is necessary. This is one of the reasons why I think it unfair of the profession and some of the public to look down their noses at ship surgeons. Such an attitude is hard to break, however. I had occasion towards the end of one voyage to give a deckhand a telling-off for failing to report for a daily dressing as ordered. He stood screwing up his woollen cap repentantly in front of me until I finished. "Well, sir," he explained, entirely genuinely, "as we was near home I thought I'd wait and go and see a proper doctor."

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Haematological Applications of A.C.T.H. and Cortisone

SIR,—May I suggest that some of the statements in the report by a special panel to investigate the haematological applications of A.C.T.H. and cortisone, as published in the *Journal* (June 14, p. 1261), should not go unchallenged? Especially is this true when it is stated that these steroid hormones, "as at present used, are not likely to have an important part to play in the treatment of disorders of the blood."

We have used A.C.T.H., cortisone, and hydrocortisone (Compound F) in a large number of cases, about 200 in all, since they were first made available for investigative purposes in the spring of 1950. We have continued to use these hormones because of their definite value in producing both specific and non-specific effects in various haematological disorders. The most striking results are obtained in acquired haemolytic anaemia of the immunological type (auto-immune haemolytic anaemia). If (1) a sufficient dosage of steroid hormone is given (up to 300 mg. of A.C.T.H. daily in severe cases), (2) in an amount sufficient to produce the well-defined so-called side-effects, and (3) for a sufficient length of time, the haemolytic process can almost always be controlled. Blood destruction usually ceases abruptly; the necessity for transfusions disappears; free antibody, if present, diminishes and often disappears; and the positive Coombs test diminishes in intensity and in some instances becomes negative. In 22 cases treated in the past two years the results may be tabulated as follows:

Complete clinical and haematological effect, with negative Coombs test	3 cases
Complete clinical and haematological effect, with persistently positive Coombs test	11 „
Incomplete clinical and haematological effect, but distinct improvement (reduction in haemolysis, no further need for transfusions, etc.)	6 „
No effect	2 „

In all except the last two cases cited, the immediate response to steroid administration was excellent and had the virtue of converting an extremely sick person requiring many transfusions to a reasonably well individual. This therapeutic method, conscientiously carried out in our clinic during a two-year period, did away with the need for splenectomy in auto-immune haemolytic anaemia. It was only after this period had been completed that two cases, both having had an incomplete clinical and haematological effect, were operated upon. Somewhat less cortisone therapy was required for maintenance after splenectomy than previously. In the hereditary types of haemolytic anaemia no beneficial effects with hormone were noted.

In the other haematological disorders the results were less constant and more uncertain. In hypoplastic and aplastic anaemia (30 cases) only one showed a striking result, although three others showed slight although definite improvement. In idiopathic thrombocytopenic purpura the results are difficult to evaluate, because certain cases are acute and self-limited, and in the chronic cases remissions and relapses often occur spontaneously. There can be no doubt, however, of the definite effect on the bleeding tendency, even without any comparable effect on the platelet count. In acute vascular purpura, which is probably an immunological disturbance, and in such probably related conditions as periarteritis nodosa and disseminated lupus, striking temporary results are often obtained; these may at times be life-saving. Although these conditions are not strictly haematological, their immunological nature probably results in their fairly frequent association with such haematological abnormalities as auto-immune haemolytic anaemia and thrombocytopenia.

In the acute and subacute lymphocytic leukaemia of infancy and childhood the steroid hormones induce a well-defined and even a complete remission in about 50–60% of the cases. If A.C.T.H. or cortisone is given simultaneously with aminopterin (15 cases), a remission may be induced in almost every case. Although in most instances the remissions are not sustained for more than two to four months, in some cases excellent and even complete clinical and haematological remissions continue for a year or longer. In chronic lymphocytic leukaemia the steroid hormones are not infrequently useful. The symptomatic haemolytic process, which is often an associated process, may be stopped and then kept under control with maintenance therapy; the myelophthisic anaemia developing as a terminal manifestation may be improved in some cases; and the generalized skin reaction of some cases (erythrodermia, exfoliative dermatitis) may be distinctly improved.

When no further course of vigorous action (*x* rays, nitrogen mustards) is possible in cases of Hodgkin's disease, lymphosarcoma, or leukaemia the steroid hormones have a distinct place in relieving symptoms, improving the appetite, and improving the patient's vitality and to some extent the status of his blood. Such therapy may result in a sufficient degree of remission to warrant the further use of chemotherapeutic or *x*-ray therapeutic procedures.

The desperate situations mentioned above usually require desperate remedies. Thus, the report of the panel, as published in the *Journal*, may be criticized in that the usual course of A.C.T.H. therapy was for only a 10-day period, and in an amount of about 1 g. (that is, 100 mg. daily), and for cortisone 1.5 g. in the same period. These doses are hardly enough by our standards. A.C.T.H. must often be given in 150–300 mg. (or in small doses intravenously) daily, and sometimes even these doses are ineffective. In four cases of immuno-haemolytic anaemia we found that the high-potency A.C.T.H. gel (Fraction D of Astwood *et al.*, corticotropin gel of Wilson and Co., Chicago) was effective when cortisone or ordinary A.C.T.H. was ineffective. Thus, the conclusions in the report of the panel, based as they are on relatively small doses of the drug given for relatively short periods, may not be entirely valid.

My chief criticism, however, of this "preliminary report" is that it seems altogether too cautious and too pessimistic. It should be noted that the central statement of the report—namely, that A.C.T.H. and cortisone "are not likely to have an important part to play in the treatment of disorders of the blood"—is qualified by the phrase "as at present used." Our own results are so dissimilar to those cited that there must be a reason and this may be it. There can be no doubt that other and better substances than the steroid hormones will probably be forthcoming, but at the present time there can be no quesion as to the usefulness of these materials in our own cases. I doubt that one can predict, nor should one be too greatly concerned, whether these agents will for evermore be important in treating disorders of the blood.—I am, etc.,

Boston, Massachusetts. WILLIAM DAMESHEK.

A.P.F. in Megaloblastic Anaemia

SIR,—Drs. H. Foy, A. Kondi, and A. Hargreaves report on remission produced by a commercial A.P.F. from aureomycin fermentation in megaloblastic anaemia of pregnancy (April 19, p. 852). They mention some possibilities as to the mechanism of this remission. We have seen similar remissions in acute leukaemia and infantile megaloblastic anaemia from streptomycin- and terramycin-derived A.P.F. (*N. Y. St. J. Med.*, 1951, **51**, 1739; *Lancet*, 1951, **1**, 1157). They have been attributed in this connexion to the antibiotic content of the A.P.F. which changes the usual proteolytic intestinal flora to a saccharolytic type. But it would now seem that one of the possibilities invoked by Dr. Foy *et al.*—that this modified flora elaborated a "maturation" substance—is ruled out by observation in one of our own cases of megaloblastic anaemia of pregnancy. This patient was fed large amounts daily of a milk culture of *Lactobacillus acidophilus* (the usual organism implanted during A.P.F. ingestion) for several weeks without intestinal tract implantation or remission, which occurred readily, however, within three days of the commencement of terramycin administration. Evidently our previous hypothesis that A.P.F. ingestion limiting proteosaemia originating from a coliform-aerogenes intestinal flora is the determinant of these remissions is borne out by this case. Circulating proteoses can also be

abrogated by plasma cholinesterase injection, which also permits remission of macrocytic anaemia (*Science*, 1948, **107**, 195).

The designation A.P.F. for "animal protein factor" has been deleted from commercial streptomyces-derived animal feed supplements in this country after it was determined that the prepotent factor therein was not the B_{12} as was originally thought but rather the residual antibiotic which these streptomyces residues contained. However, the term had already got into the clinical literature, as evidenced by Drs. Foy, Kondi, and Hargreaves's report as well as several of our own. It is now known that many other substances beside antibiotics and B_{12}, when fed at optimal dosage levels, act like "animal protein factor" in increasing the growth rates and "livabilities" of poultry and hogs, just as they may induce remission in certain cachectic diseases. For example, cortisone, arsenicals, polysorbates ("tweens"), androgens, chlorophyllins, cinchona, and colchicine derivatives, as well as many organic acids, may on occasions act as A.P.F.s in the original sense on domesticated animals, and the use of all of these materials as "alteratives" in humans for many years attests to some observed powers toward the reversal of a cachectic trend. Some of these substances cause direct modification of the intestinal flora; the others apparently limit the permeability of the intestinal wall through the mediation of the adrenocorticotropic mechanism.

The latest excellent example of an A.P.F. is isoniazid, which definitely acts as an "alterative" in many non-tuberculous conditions. Like the streptomyces-derived antibiotics, it may induce rapid flesh gain in patients with inoperable malignancy as it does in poultry under proper conditions. The designation A.P.F. has therefore become a useful one to represent a class of substances, and we have suggested that it be retained to connote a new term "anabolism promoting factor(s)." If others have a more appropriate designation for this class of therapeutic agents, we should be happy to have it supersede ours.—We are, etc.,

ROBERT D. BARNARD.
LOUIS R. ORENS.
MAX SCHWARTZ.

New York.

Basal Metabolism in Hypopituitarism

SIR,—The contents of the second sentence of the first paragraph of Dr. M. H. Oelbaum's letter (August 23, p. 445) are not actual records of the open-circuit method for the B.M.R. determination. Actual records (none of which were given) are generally understood to be the volume of the expired air relative to time, analysis of that air, the respiratory quotient, and the height, weight, age, and sex of the patient.

The peculiar B.M.R. results reported by Dr. Oelbaum may partly be explained by his use of the Sanborn standards. These so-called "standards" were condemned by W. H. Stoner (*Boston Medical and Surgical Journal*, 1923, **189**, 236) as hybrid—and rightly so. Stoner pointed out errors in the tables. In fact, these tables were not even based on actual observations. Stoner concluded that all results calculated on the Sanborn tables should be excluded from the recognized legitimate data on B.M.R.s. Dr. Oelbaum's metabolism rate results in hypopituitarism are a striking confirmation of the views set forth by Dr. Stoner some 30 years ago.—I am, etc.,

London, W.1. J. DOUGLAS ROBERTSON.

Positive v. Negative Prints

SIR,—It seems a pity, and is certainly confusing, that Mr. A. P. Bertwistle (August 23, p. 446) has reopened the positive *v.* negative (facsimile) question. There is really no controversy at all, but only a certain amount of misinformation.

The heresy that the positive is better because it involves fewer processes and less loss of definition dies hard, but it is a fact that the facsimile reproduction is capable *in skilled hands* of producing a far more accurate result than the simple positive. Prints for publication should not be entrusted to unskilled hands. Where quality is demanded (and the vast bulk of radiographs are printed so that they may be made into half-tone blocks—a far more costly process than the photographic printing) cost should not be a consideration. In any case, the time of a skilled worker is worth far more than the materials involved.

As to Mr. Bertwistle's first point, this is debatable. The only people who see a positive image, where densities appear dense, are fluoroscopists; they constitute a minute proportion of those who use radiographs. The remainder work always in the negative convention, and all *my* clinical colleagues, and many students to whom I have talked, prefer to stick to that one convention. The radiograph is in any case a convention, a two-dimensional shadowgraph.

Finally, it is quite untrue to say that the *Year Books* will not abstract papers with facsimile reproductions (at least, that is how I read the sentence). I have to-day sent five facsimile prints which they requested from a paper in the *British Journal of Radiology*. If, however, Mr. Bertwistle means that they turn down mixtures of positive and negative, then we are in agreement, though our solutions differ.

I have endeavoured to survey the problems of radiographic presentation in a paper to the *British Journal of Radiology* (in press). The subject is complex, and too long to cover in a letter.—I am, etc.,

Manchester, 20. ROBERT OLLERENSHAW.

The Perennial Peptic Ulcer Palaver

SIR,—The letter from Sir Robert Hutchison (August 30, p. 513) must delight those who like to see a sharp pen used for the writing of good sense and good prose, as well as for puncturing balloons. The long-term success of a gastro-enterostomy is largely dependent on the skill of the carpenter (and, personally, I have never seen an abdominal surgeon who approached Sherren in this respect), but even when only adequately performed this procedure gives such eminently satisfactory results that it would be a pity if its continuing performance were to be sacrificed to the Athenian desire of modern surgeons for some new thing. I can only report on such a small clinical experience as comes to one practitioner over a period of 25 years, but I do not doubt that others with longer and larger opportunities for observation will feel the same.

With the possible exception of sex, more nonsense is talked about diet than any other subject, and in my experience peptic ulceration is no more related to food than is gout to alcohol or baldness to brains. Surely Alvarez has shown conclusively the value of the remark of the bishop to the frightened curate who was expressing his inability properly to feed his Lordship at his visitation: "But, my dear boy, I never mind what I eat, as long as it is of the best quality, and perfectly cooked." I am sure that, with the exception of those foods which act as idiosyncratic poisons, such as mushrooms, shellfish, onions, radishes, or eggs, there is much truth in the aphorism that the major part of digestion takes place in the kitchen.—I am, etc.,

London, W.1. R. CHRISTOPHER HOWARD.

SIR,—It was indeed a pleasure to read a letter from Sir Robert Hutchison (August 30, p. 513) with his profound sense of values, his humour, and his wisdom of long experience. Indeed, I believe a letter from him each week in your *Journal* would have the same tonic effect on the medical profession as the Radio Doctor's early morning talks used to have on the general public. It would be presumption on my part to say that I have a certain amount of fellow feeling for those eminent men to whom Sir Robert directed his corrective, but 25 years ago, as a clerk on the renowned firm of Hutchison and Rowlands, he used to correct errors of spelling in my medical histories.

For my own part I believe there are causative factors, both in peptic ulcer and, indeed, ill-health in general which we probably in ignorance ascribe to "overwork" and "frustration." For some time I have been interested in this problem, and when a patient came to me and said, "I can't sleep, I don't eat, I won't work, doctor," I was inclined to reply, like Robb Wilton, that those are exactly my symptoms and I wonder what is the matter with us both. Or when women come to me and say, "When you are at the change, doctor, you do feel awful, don't

you?" I reply with feeling, "I do, I do." Life is certainly becoming more difficult. Even the hypochondriac can have little pleasure in his illness, for with the enormous increase in remedies there is the constant anxiety lest a cure be found for his particular complaint.

My opinion is that this problem is not psychological but philosophical. I have found, in this country practice, that my patients have required my help at a regularly increasing rate during the last 17 years, and the war years and the Health Service did not alter this regular yearly increase with approximately the same number of patients. Moreover, it seems to take me longer and longer to do less and less. The attitude to life which appears to be almost universal is increasingly based on the attitude, "Why should I have to do this?" or, "Why shouldn't I have that?" and we are so busy asking these questions, to which we do not wish to have the answers, that it leaves us with little time for anything else. As Sir Robert would say, it is a mentally constipating and physically exhausting process.

Patients, for instance, are wondering if they are receiving all that they have paid for, and this provokes the attitude, "Am I being paid for all that I am giving them?" As one of my patients so truly remarked on the advent of the shilling charge for prescriptions, "We was better off as we was before this scheme." He was quite right, for I had sent him numerous accounts in the good old days and he never paid any one of them. But in those days he did repay me with gratitude.

"Frustration" and "overwork" are banished by happiness, and I believe happiness is a result of giving and receiving rather than buying and selling. I would therefore suggest that these factors are philosophical and are incorrectly referred to as psychological problems. I should be grateful to learn whether philosophers undertake therapeutic measures, or do they merely utter aphorisms. For my own part, with my limited experience, I have yet to find a patient who has been cured by psychological methods unless the treatment included electric shocks.

That famous philosopher of the old music halls, Marie Lloyd, gave some useful advice, but more recently Mae West was on a more solid foundation when she said, "Take it easy, big boy, you'll last longer."—I am, etc.,

Boston, Lincolnshire. N. J. BEE.

A Gastric Gossip

SIR,—Your issue of Saturday, July 19, has just reached me, and I read with great interest Sir Arthur Porritt's gastric gossip (p. 107). It would be important to substantiate the statement that peptic ulcer is a rare condition in the black races. First, one must take into account the considerable variations in disease among the races within the race—due to epidemiological, climatic, sociological, and tribal differences—even within the single political entity of an enormous country like Nigeria. Secondly, what we see in our hospitals may or may not be typical of the world outside in village and bush. In our tropical institutions we touch only the fringe of the problem of health and disease. Some people like coming to us like those of the western region; others, like the tradition-bound Hausas, avoid us, as we are reminded in passing their village streets filled with bodies of the crippled and diseased. What can be said, however, is that in our hospital at Ibadan the peptic ulcer problem is very much with us and that for the past year numerous and severe cases have come for operation. In fact, peptic ulcer is the outstanding abdominal complaint—acute abdominal cases apart—and rivals in frequency the cases of complications of parasitic infection.

As for a "hectic environment," tropical man's struggle for existence may be as hectic as anybody's; the idea, however, that the "speed around him" has anything to do with our problem does not apply in Africa, and seems to me to have become just a phrase in our books and dissertations. Maladjustment to the struggle—yes, perhaps, but speed—in equatorial Africa? One final word on the advice to transfer the dyspeptic from "ulcer-prone countries" to tropical regions. A journey to Africa will benefit everyone, but it would hardly be specific treatment. In nine months I have dealt professionally with six Europeans (out of a small community) in various phases of the ulcer trend. A long-standing member of our College who had a gastrectomy, and the tragic death of an "old coaster" in Government service who refused to have himself pensioned off in order to stay the course prescribed for a full pension and who eventually perforated, come especially to mind.

It should be borne in mind that only very slowly does the unemancipated African find his way into our care and statistics; any generalization on what does and what does not occur, and occur frequently or otherwise, in the "black races" must await the results of patient, thorough, and prolonged collection and analysis of data so far utterly lacking.—I am, etc.,

University College, Ibadan, Nigeria. PETER KONSTAM.

Resuscitation with Hand-bellows

SIR,—The article by Dr. E. J. Gordon Wallace on resuscitation (August 2, p. 278), and the Ministry of Supply notice on the treatment of nerve gas casualties (August 9, p. 334), will surely be of great practical interest to all first-aid and Civil Defence workers. Could not the small hand-bellows illustrated in the M.O.S. circular also be used for the resuscitation of drowned persons and patients with asphyxia due to fire, coal-gas, and electrocution? A case was recently reported in a daily newspaper of a nurse who used mouth-to-mouth breathing and resuscitated an apparently moribund infant—surely the same principle is involved in the use of the bellows. I believe that on some anaesthetic machines the bellows can be utilized to give atmospheric air in an emergency. There may be reasons why the bellows could not be used by first-aid workers in this way—for example, fear of over-ventilation—but it would be interesting to have the views of experts on this seemingly simple method of resuscitation.—I am, etc.,

London, E.7. J. A. COPPING.

Aetiology of Rheumatic Diseases

SIR,—Dr. T. W. Lees (August 16, p. 363) reports experiments on rabbits in which a decreased skin reaction to an injected foreign protein was found in animals rendered myxoedematous by thyroidectomy. From this observation and selected observations of others he argues that the endocrine theory of the aetiology of rheumatic diseases is not plausible and that the effects produced by A.C.T.H. and cortisone acetate are those of non-specific toxic substances.

The arguments that he brings forward are so full of fallacies and the observations that he quotes susceptible of so many interpretations that it would require more than a letter to deal with them. The subjects into which he plunges may perhaps be somewhat clarified by stating these three facts. (1) The effects produced by A.C.T.H. and cortisone, like those produced by other physiological substances, depend upon the amounts administered and the state of the body receiving them. The effects of excess are deleterious, as are those of deficiency. This applies equally to such substances as common salt and insulin. (2) There is so much that remains unknown about the metabolism of hormones that it is unwise to argue that there is or is not a defect in their metabolism in this or that form of rheumatism or cancer. (3) For more than one and a half years now, at certain centres in this country and in the United States, cortisone acetate has been given continuously in the treatment of rheumatoid arthritis in daily doses averaging 62½ mg. (for adults). So far we have no proof that such dosage has interfered with normal body function or resistance to infection.—I am, etc.,

Sheffield, 3. H. F. WEST.

Trials of Antihistaminics

SIR,—Dr. O. A. N. Husain's interesting report (August 9, p. 337) prompts me briefly to mention some of our observations of the effect of a potent antihistaminic—namely, "phenergan" (promethazine-hydrochloride)—on micro-organisms *in vitro* and in experimental animals. The antibacterial properties of phenergan were presumably first

studied by Leduc,[1 2] who found that in a concentration of 0.5% it was active against *C. diphtheriae, Kl. pneumoniae, Salm. typhi, Staph. aureus, Str. haemolyticus,* and *Shigella flexneri.* We have tested 503 strains isolated from the ear and the upper respiratory tract on routine cultivation. The agar-ditch technique was employed and two concentrations of the drug, 125 and 500 μg. per ml. of agar, used. It may suffice to mention that almost all streptococci—alpha or beta haemolytic—(109 strains) and pneumococci (7 strains) were sensitive to 125 μg. per ml. and the majority of the strains of *Staph. aureus* (172 strains, 83 penicillin-resistant) were sensitive to 500 μg. per ml. of the antihistaminic. Gram-negative bacilli, on the other hand, with the exception of *Bact. coli,* showed resistance to the concentrations used. Like Dr. Husain, we have also been disappointed by the resistance of *Ps. pyocyanea* and *B. proteus,* organisms so frequently encountered in chronic infections of the ear and external otitis, in which a combined anti-allergic plus anti-bacterial agent would be of therapeutical value.

In apparent contradiction to its antibacterial properties Halpern and associates have noted that phenergan promoted the generalization of a localized subcutaneous infection due to *Salmonella typhi-murium* in rabbits,[3] or the emergence of spontaneous autogenous fatal injections in healthy guinea-pigs treated with excessive doses of phenergan (25 mg. per kg.).[4]

Our results are summarized as follows: (1) Subcutaneous injections of 50 mg. in 2 ml. of phenergan daily into the flanks of 12 rabbits (total amounts 30–50 ml.) failed to promote the spread of a localized subcutaneous abscess produced by the subcutaneous injection of 1 ml. of a saline-suspension of *M. albicans.* The strain used killed a rabbit in three to four days when injected intravenously, producing multiple miliary monilial foci in the kidneys and myocardium. Subcutaneous injections produced only a self-limiting subcutaneous abscess which healed up spontaneously in 14 to 21 days. This course of events remained on the whole unaffected by phenergan, though it caused extensive necrotic changes at the site of the injections. These healed up, provided the process did not reach the abdominal or thoracic cavity.

(2) Subcutaneous injections of phenergan into the abdominal wall of 11 healthy guinea-pigs once or twice a day, 25 mg. per kg. (total 10–30 ml., or 250–270 mg.), caused death of the animals in about three weeks or less. This, however, appeared to be due to the direct toxic action of phenergan, which caused extensive necrotic changes in the tissues of the abdominal wall with widespread degeneration of the abdominal muscles, leading in most animals to diffuse adhesive peritonitis, perisplenitis, and perihepatitis. There were adhesions between the liver and intestines not unlike those described by Falconer and Derrick[5] in mice and guinea-pigs following the intraperitoneal injection of mercurial preparations. The irritant action of phenergan on the peritoneum was extensive, though it was not injected directly into the peritoneal cavity.

The emergence of spontaneous infections or the generalization of localized induced infections under the influence of various means is a recognized phenomenon. The cultural results in our experiments were not convincing and frequently negative. But it would not be surprising if owing to the described effects of phenergan the resistance of the animals to infections, spontaneous or otherwise, were reduced. Equally the necrotic change in the tissues caused by phenergan may contribute to the spread of certain subcutaneous infections experimentally induced.

I am glad to thank Mr. A. Crichton, New Products Division, Messrs. May and Baker Ltd., for the supply of 10 grammes of phenergan and abstracts of relevant publications.

—I am, etc.,

London, W.C.1. I. FRIEDMANN.

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Antihistamines and Treatment of Burns

SIR,—I was much interested in the article by Dr. S. Sevitt *et al.* (July 12, p. 57) on the failure of an antihistamine drug to influence the course of experimental human burns. The probable reason for this failure is that an antihistamine, administered orally, is not sufficiently quick-acting to oppose the increase in capillary permeability before it becomes irreversible. Dr. A. J. Levine, who has reported remarkable results with an antihistamine cream (*Journal,* 1951, **2**, 300), has found no effect on the development of redness and blistering if the cream was applied four hours or more after the burn had been sustained. This probably represents the critical period, after which changes in the capillary bed become irreversible.

The investigation of Dr. Sevitt and co-workers leaves no doubt about the failure of an orally administered antihistamine. Before long carefully controlled experiments may be carried out to determine whether, in such cases, an antihistamine applied locally in the form of a cream will be more effective than when administered orally, and the results will be awaited with interest.—I am, etc.,

Madras. G. G. KRISHNAMURTY.

Ichthyosis and Hypnosis

SIR,—The case of ichthyosis reported as cured or ameliorated by hypnotic suggestion (August 23, p. 422), though of the greatest interest, should cause in many respects little surprise. On the basis of observations in an allergy clinic during the last 30 years I have unhesitatingly classified ichthyosis as one of the allergic disorders, together with hay-fever, asthma, etc.; these, as I have stated, are all affected for good or ill by the emotions, moods, and nervous tensions of the patient. If hypnosis can change these emotions, it should change the likelihood of allergic symptoms, including those of ichthyosis.

Again, it is to be expected that the grafting of healthy skin on to an allergically affected area would fail in its purpose. An essential factor of an allergic response in the skin resides not in the skin of that patient but in his blood—as is amply shown by the well-known Prausnitz reaction. What does seem strange, at least to one ignorant of the physiological mechanism of hypnosis, is that the skin improvement was in the first experiment confined to the area (left arm) mentioned in the prayers or commands of the hypnotist. It would be interesting to know how closely the amelioration was in the first experiment confined to this area; the photographs do not show this clearly.—I am, etc.,

London W.1. JOHN FREEMAN.

The Intern Year

SIR,—Few clinically inclined graduates could possibly condemn the advantage of the intern year. It is due to the absence of any comments in your leading article (August 30, p. 481) on the status of those contemplating careers in the preclinical sciences that I put the following facts at your disposal.

The method of entry of the medical graduate into preclinical appointments is at present achieved by completing a degree of B.Sc. in natural science. The time required to complete the B.Sc. course ranges from one year (anatomy, physiology) to two and three years (biochemistry, bacteriology, genetics, etc.) in addition to the now standard six-year medical curriculum. The position of the anatomy or physiology graduate with respect to the intern year depends on his attitude. If he wishes to pursue a strictly scientific career in either of these he may neglect the intern year. If he wishes to maintain close liaison with clinical surgery or medicine the intern year is necessary, desirable, and in this instance does not extend his complete course beyond eight years. However, in the case of medical graduates wishing to spend two to three years studying for the B.Sc. in biochemistry, bacteriology, etc., the majority, desiring as they do to combine a thorough knowledge of the science of their choice with a medical qualification which, though adequate, is not too heavily biased clinically, will find the intern year necessary for registration a heavy incubus, unless it is indicated by some very cogent reason, since it extends the number of years spent after medical graduation to from three to four to nine to ten years in all.

It seems to me that a medical curriculum of six years' duration, especially if combined with vocational residencies and clerkships, should be considered adequate for full registration. The M.B., Ch.B., B.Sc., only provisionally registered, cannot gain commissioned rank in the period of his Army service, and he is deprived an opportunity of carrying on with his vocation during conscrip-

tion, whereas this privilege is accorded to his clinical brethren who have won their full registration by the expenditure of one year, which, in relation to the amount of useful clinical knowledge gained, is trivial to them, although to the already over-burdened preclinical man it may well be the last straw.

All medical graduates will differentiate into either clinicians or "preclinicians." The Medical Act, 1950, concerns itself only with the welfare of the clinicians, to whom it grants the privileges of registration in return for a term of clinical internship, this presumably to ensure their clinical competency. What seems unfair to me, however, is that all graduates, whether potential clinicians or preclinicians, must serve a term of purely clinical internship. This will be to the advantage of the former, but frustrating to the latter, who will rapidly become inept in matters relating to the science of his choice.

Surely the Medical Act, 1950, would be fairer if the privilege of registration were granted to the preclinical man in return for a year's work in an approved preclinical establishment, where he could become as adept at his work as a clinical houseman could be at the termination of his intern year.—I am, etc.,

Glasgow. STEWART FLETCHER.

Danger from Endotracheal Tubes

SIR,—Dr. C. F. J. Baron (August 16, p. 391) rightly draws attention to the danger of asphyxia caused by the cuffs on endotracheal tubes, and in this connexion the following case which occurred in my own practice may be of interest.

A healthy male, a labourer, aged 37 years, and weighing 9 st. 10 lb., was admitted for a left radical mastoidectomy. For premedication he was given pethidine 100 mg. and hyperduric atropine gr. 1/100 (0.65 mg.) one hour before operation. Anaesthesia was induced with 10 ml. of 5% thiopentone, and after injecting 80 mg. of "flaxedil" he was intubated orally with a No. 9 cuffed endotracheal tube. Anaesthesia was maintained with N_2O and O_2 (30%) supplemented with 50 mg. of intravenous pethidine. This appeared to have little effect and after five minutes a second 5 mg. of pethidine was given by the same route. The semi-closed circle absorption technique was employed. The operation proceeded smoothly for about 15 minutes, when unfortunately the patient slipped a little down the table, altering the position of the head. The operation was suspended while the patient was lifted up the table and anchored in position again. The operation recommenced, but on pressing the reservoir bag it was found impossible to ventilate the patient. It was first thought that the tube had kinked in the pharynx, but this was found not to be so. The anaesthetic circuit from the pharynx to the machine was then checked and found to be in order. By this time the patient had become cyanosed and his pulse was fading. The surgeon was informed that the airway was obstructed and removal of the towels brought the pilot balloon of the cuffed tube into view, and on deflating it a perfect airway was restored. By this time, however, approximately three minutes after the airway first became obstructed, the heart had stopped. The table was placed in a slight Trendelenburg position and the surgeon carried out cardiac massage forthwith. Artificial respiration with pure oxygen was performed and 15 mg. of methedrine injected into a vein. The surgeon confirmed that the heart had stopped and that the myocardium was toneless. After performing cardiac massage for approximately one minute tone returned and shortly afterwards the heart started to beat, the pulse became palpable at the wrist, the patient's colour became pink, and spontaneous respiration returned.

The operation was completed, but a simple rather than the planned radical mastoidectomy was performed. On leaving the theatre the patient's blood pressure was 80/55 and his pulse was regular at 100 a minute. His reflexes were not as brisk as one would have liked and the endotracheal tube was left in situ and oxygen administered through it. The foot of the bed in the ward was elevated and he was placed on a quarter-hourly blood pressure and pulse chart. One hour after his return to the ward his blood pressure rose to 105/75, his pulse was regular at 96 a minute, his reflexes were brisk, and the endotracheal tube was removed. Three hours after his return to the ward his blood pressure was 120/85 and his pulse was still regular at 96 a minute, but he remained unconscious. During the next few hours he became very restless and was completely disorientated. He was controlled with paraldehyde and a slow intravenous drip was set up. Atropine was given as a prophylactic against pulmonary oedema. An almost maniacal state persisted for nearly 48 hours, after which time he gradually settled down and began to understand what was said to him. Retrograde amnesia persisted for a whole week, but he eventually made an uneventful recovery. Subsequent *x* rays of his chest and heart were normal, and an E.C.G. was within normal limits throughout. My thanks are due to Mr. R. R. Simpson for his permission to report this case, and for the speed and skill with which he performed the cardiac massage.

In conclusion there are a few points I would like to stress. The cuff of an endotracheal tube should first be tested for leaks and herniations by inflating it prior to use inside a glass test-tube 2 cm. in diameter, and observing the pressure required to ensure a gas-tight fit. If faulty the tube should be discarded. Initial inflation of the cuff in the trachea should be moderate and adequate only to produce an airtight circuit, as the pressure of the inflating air, in accordance with its coefficient of expansion, will rise as it reaches body temperature.

In deference to Dr. Baron I consider the manufacturers who are shortening the part of the tube beyond the cuff are carrying out an improvement. The lengths of some cuffs, together with that part of the tube beyond, have in the past been such that when the proximal end of the cuff has been just beyond the cords the distal end of the tube has been at the carina or beyond. Finally, I would suggest that the obstruction be immediately relieved, not as Dr. Baron advises by pushing the tube further into the trachea, which may be impracticable or unwise, but by the simple deflation of the cuff.—I am, etc.,

Hull. W. N. ROLLASON.

Diabetics and Road Safety

SIR,—Motor accidents have very rarely occurred when diabetics who are taking insulin are suffering from hypoglycaemia. This condition may arise from several causes, such as omitting to eat the necessary carbohydrate at the usual time—that is, at breakfast, in the middle of the morning, at the midday meal, at teatime, or at the evening meal. If the carbohydrate is either omitted or delayed, a severe reaction may occur owing to unopposed overaction of the insulin. A hypoglycaemic attack may also be produced by taking unusual exercise shortly before the car is driven, or as a result of changing a wheel.

The Medical Advisory Committee of the Diabetic Association therefore asks all doctors looking after diabetics taking insulin and driving motor-cars or riding motor or pedal cycles to make certain that their patients understand the possible causes of hypoglycaemic attacks and how they can be prevented by regular intake of carbohydrate at the usual meals, which should be taken punctually. Some extra carbohydrate should be eaten both before and after any unusual exercise. A supply of biscuits or 12 lumps of sugar or glucose should always be carried in the car or cycle in case a meal is unavoidably delayed or unexpected exercise is necessary.

The Committee especially hopes that, if a doctor knows that a patient sometimes does not recognize the symptoms of hypoglycaemia, he will advise his patient not to apply for a driving licence.—I am, etc.,

R. D. LAWRENCE,
Chairman, Medical Advisory Committee, Diabetic Association.

London, W.1.

Three Cases of Weil's Disease

SIR,—Dr. Alan A. Morgan, reporting three examples of Weil's disease (August 23, p. 427), rightly stresses that the diagnosis should be considered even in the absence of any obvious exposure to the infection. In two of Dr. Morgan's cases care in history-taking revealed that there had been exposure to leptospiral infection; in these two patients the picture of classical Weil's disease is described, and the diagnosis receives ample laboratory support.

In Dr. Morgan's second case, however, no history of possible infection could be traced, and it would appear that here the diagnosis has been based upon slender evidence, while some of the laboratory findings would be unusual in Weil's disease. The

illness was afebrile. Though not unknown, such cases are rare enough to raise doubts. With jaundice established, the white-cell count is normal. In the absence of jaundice, normal white-cell counts are quite usual. Once jaundice has developed, a polymorph leucocytosis, as noted in Cases 1 and 3, is probably constant, and provides help in the differential diagnosis.

A blood urea of 19 mg. % is recorded: in all forms of leptospiral infection there is some degree of nitrogen retention, and may of course, as in Case 3, be extreme. When the usual tests for liver function are applied in Weil's disease, even where jaundice is very severe, it is striking to find how little these depart from normal. This observation has been frequently confirmed, and remains unexplained as far as I know. In Dr. Morgan's second case the thymol turbidity test is recorded as positive at 8 units, while the serum alkaline phosphatase is very high at 53 units. Another important and again unexplained observation in classical Weil's disease relates to the level of the serum cholesterol. Low figures are the rule, and in a recent personal case with a serum bilirubin of over 60 mg. % the serum cholesterol fell to below 50 mg. %. Dr. Morgan records 225 mg. % serum cholesterol. In none of these laboratory tests have we anything to support the diagnosis made, and it appears that the diagnosis was in fact made as a result of one agglutination test, carried out on blood obtained on the fifth day of the illness. This serum, at a dilution of 1:300, agglutinated a suspension of leptospires. It is unusual to obtain a positive agglutination reaction on the fifth day, certainly at so high a titre, while there is no doubt that, following a previous unrecognized infection, the agglutination test remains positive, often for several years. If a second agglutination test had been carried out on this man's blood, and if this had revealed a rising titre, then the diagnosis could have been accepted, and the unusual laboratory findings would have been noteworthy and important.

These observations are not made in any spirit of criticism, but they seem to me to raise a number of important aspects of diagnosis when faced with this by no means uncommon infection.—I am, etc.,

Southampton. KENNETH ROBERTSON.

Honorary Medical Officers to Amateur Boxing Association

SIR,—We are anxious to obtain the voluntary services of medical men as medical officers to attend amateur boxing shows in London and the suburbs during the coming autumn and winter. The shows usually take place in the evening, and the duties consist in examining the contestants (total time half to three-quarters of an hour) and being available or on call for any serious injuries, which are usually very few in number. The only recompense we can offer is a good boxing show and a convivial evening. Medical officers will have the satisfaction of knowing that they are assisting to advance, foster, and encourage a high physical and moral standard in the health of the youth of the nation.

Will doctors who are interested please write to me at the London Amateur Boxing Association, 69, Victoria Street, London, S.W.1 ?—I am, etc.,

London, S.W.1. J. L. BLONSTEIN.

Admission of Poliomyelitis Cases to General Hospitals

SIR,—I am greatly interested to read the letter by Dr. Howlett Kelleher in this week's *Journal* (September 6, p. 562). Dr. Kelleher is, I believe, recognized as one of the leading experts on poliomyelitis in London, and it is natural that cases of this disease should gravitate towards the hospital of which he is superintendent.

What to me—and, I think, to others of my colleagues when they hear it—is almost incredible is that it is to this very hospital, the Western Fever Hospital, that the South-west Metropolitan Regional Hospital Board intends to transfer the in-patient department of the Metropolitan Ear, Nose, and Throat Hospital. I need hardly say that the surgical staff of this famous old voluntary hospital—the oldest ear, nose, and throat hospital in the world—have been fighting this idea with every weapon they possess, ever since it came to their notice. The following resolution, for example, was passed unanimously at the meeting of the medical staff committee of the Metropolitan Ear, Nose, and Throat Hospital so long ago as June 27, 1950: "That this medical staff committee felt that it could not take the responsibility of operating on and nursing ear, nose, and throat cases within the precincts of a fever hospital."

I was told by one of the senior administrators that it would be quite all right because the word "Fever" was to be omitted from the title of the Western Fever Hospital, and, indeed, I see that Dr. Kelleher addresses his letter from the Western Hospital. Dr. Kelleher himself told me that it was intended to place the ear, nose, and throat cases in the next block to that housing the poliomyelitis cases—but, he assured me, there was no danger of infection. Nevertheless, it is a fact that two or three years ago our hospital management committee *ordered* the surgeons to stop all operating on ear, nose, and throat cases in children for five months, because there was an outbreak of poliomyelitis in London.

The regional hospital board has repeatedly refused to discuss the matter with our medical staff or to receive a deputation. I should very much like to know on what grounds it is suggested that there is no danger of these ear, nose, and throat patients catching poliomyelitis—a disease of which we have no precise knowledge of the method of infection. I understand that the move of our in-patients to the Western Fever Hospital (which is situated, I believe, in a cul-de-sac somewhere in the back end of Fulham) is to take place "in the near future," one of the reasons being, I gather, that the administrative staff of our H.M.C. has laid covetous eyes for a central office upon our present well-equipped in-patient department, which has an excellent operating-theatre, many separate rooms, and no room with more than five beds in it, a lift, and a comfortable nurses' home, with gardens in front of it and behind it, conveniently situated with two 'bus routes and two underground stations near. Need you wonder, Sir, that I am disturbed about this subject of poliomyelitis and infection, especially with regard to ear, nose, and throat cases ?—I am, etc.,

London, W.1. R. SCOTT STEVENSON.

SIR,—My answer under "Any Questions ?" (August 9, p. 349) has provoked some sharp rejoinders, some of which I now realize were deserved. However, I feel that your correspondents evade the main problem.

I had, of course, no intention of questioning the excellence of the treatment and facilities which must be available in large infectious diseases (I.D.) hospitals such as the Western. But in many parts of the country the provision of sufficient nurses for smaller fever hospitals is causing great anxiety, while many lack equipment such as, for example, portable *x*-ray apparatus, which is desirable for the supervision of some cases. Under these circumstances paediatricians and others must ask themselves whether it is justifiable to send cases of poliomyelitis into a grossly understaffed I.D. hospital when greatly superior nursing and hospital facilities are available in a near-by general hospital. Many paediatricians and physicians have treated scores of cases of poliomyelitis in general wards without cross-infection occurring, and indeed, as Dr. A. H. Gale infers, the need for advising treatment in I.D. hospitals is based more on theory than experience. The cases he quotes cannot be considered to decide the matter, so am I not then justified in repeating that in the present state of our knowledge "the interests of the patient should take priority over the theoretical slight risks to others which are involved in sending the patient to a general rather than a fever hospital ?"

In many places, including, of course, the regions of your distinguished correspondents, the patient's interest demands admission without question to the I.D. hospital, but when this is not so, what then ? Are your correspondents prepared to say that these cases must go to an I.D. hospital whatever the risks to the patient ?—I am, etc.,

"YOUR EXPERT."

Obituary

Sir HUGH CAIRNS, K.B.E., D.M., F.R.C.S.

We are indebted to Dr. MICHAEL GELFAND, of Salisbury, Southern Rhodesia, for the following appreciation: I would like to add my humble tribute to the late Sir Hugh Cairns, whom we had the privilege of welcoming to Salisbury in 1948 as first Sims Professor. On his arrival, although he was staying only three days and had numerous engagements, he readily accepted our invitation to lecture to the B.M.A. He expressed a wish to visit the Native Hospital. He was told it was an old one, but he chose it in preference to the European Hospital, since he felt the latter would differ in no marked aspect from any other modern hospital. He emphasized that it was not the building he wished to see but the work in it.

Early the first morning he arrived at the hospital and proceeded to see each case in turn, examining many of the patients himself and asking numerous questions about the natives, their prevalent diseases, diet, and customs. Everything interested him. To our great surprise he returned in the afternoon—one of our hot Rhodesian afternoons—to continue the round. Never before had we seen such enthusiasm and energy in a visitor. In the surgical ward he encountered a young patient complaining of severe abdominal pain and distension. As yet the diagnosis was uncertain, and this worried Cairns. Late the following afternoon, unbeknown to us, he made a special visit to the hospital to see this patient once more. It was subsequently shown that he was suffering from a splenic abscess, an interesting tropical entity which Cairns was unlikely to have seen before but which to his trained eye was unusual, and his peace of mind must have been disturbed by this problem.

Cairns taught us that every illness is worthy of research and that in any subject, no matter how well known in medicine, inquiry is always worth while, as one is almost certain to be rewarded by the elucidation of some new fact or aspect.

We took great pleasure in his meeting with Sir Godfrey Huggins, our Prime Minister: each great Fellow of the College of Surgeons was so pleased to meet the other, each aware of the other's contribution in his own particular sphere. Cairns lived these three days in Rhodesia fully, enjoying every moment of his crowded visit. He was obviously in love with the country and its people. This love probably had its origin many years back in his gratitude to Cecil Rhodes for the scholarship which perhaps was the beginning of his distinguished career.

Dr. A. G. L. READE, who died on August 17 at Ipsden, Oxfordshire, at the age of 70, came of an old Oxfordshire family. He was the second son of Arthur Edward Reade, who, after serving in the Indian Civil Service, became secretary-superintendent of Charing Cross Hospital. Arthur George Lawrence Reade was educated at Dulwich College and at Charing Cross Hospital, qualifying M.R.C.S., L.R.C.P. in 1905 at the age of 22. After holding various house appointments at Charing Cross Hospital he became senior house-surgeon at the Radcliffe Infirmary, Oxford, and then house-physician to Sir William Osler. When, in 1908, the Metropolitan Asylums Board opened Queen Mary's Hospital for Children, Carshalton, he was appointed senior resident, and there began his lifelong interest in childhood tuberculosis in all its forms. From 1912 to 1920 he was an assistant medical officer in the public health department of the London County Council. Dr. Reade served through the 1914–18 war as a surgeon lieutenant in the R.N.V.R. in the South Atlantic, at Chatham Barracks, and with the Grand Fleet, and was awarded the O.B.E. for his services. In 1920 he became medical superintendent of New End Hospital, Hampstead, where his diverse capabilities were fully utilized in emergency surgery, obstetrics, general medicine, and in administration, for which he had an outstanding gift. From 1930 to 1933 he was a senior medical officer at County Hall, assisting in the reorganization of the municipal hospitals and the outdoor medical work for the County of London. He reverted with great content to hospital practice as medical superintendent of High Wood Hospital for Children at Brentwood, Essex, then constituted for the treatment of rheumatism and pulmonary tuberculosis. In September, 1939, High Wood received general orthopaedic cases, and an E.M.S. hospital built in the grounds greatly added to the scope of Dr. Reade's responsibilities. In 1942, to his great satisfaction, he was recalled by the Admiralty and was appointed principal medical officer at H.M.S. *King Alfred*, with the rank of surgeon captain, a post for which he was admirably qualified both personally and professionally. On demobilization he returned to High Wood for a further two years, retiring at the age of 65 to live at Ipsden. For a time he undertook duty with the Ministry of Pensions and also with the Oxford Regional Hospital Board, until, in 1949, a coronary thrombosis obliged him to give up. He continued, however, to take an active part in local affairs, being secretary of the Ipsden parochial church council and a churchwarden, a manager of the village school, and, for a time, chairman of the local branch of the British Legion. From all these activities he will be greatly missed. He was attending matins on Sunday morning, August 17, at Ipsden Church when a second coronary thrombosis occurred which he did not survive. Dr. Reade had many interests, both cognate to and outside his profession. He was for many years an examiner for the General Nursing Council. From student days he was deeply interested in the welfare of working lads, and for a time he lived at the Oxford and Bermondsey Club, with which he kept up his association. He was a devout churchman, and served as a lay reader in every diocese in which he lived. He was also a past master in masonry. He married in 1917 Dr. Violet Newmarch, who survives him with one son, Captain A. H. N. Reade, and a daughter, who is the wife of Dr. John Penistan.

W. J. R. writes: Dr. Reade possessed an unbounded enthusiasm. He actively supported and encouraged all activities of the younger generation. He was for many years vice-chairman of the Brentwood Boy Scouts Association. He was a popular umpire at local school swimming contests and he also acted regularly as a referee, and with more than average proficiency, at the local regimental boxing contests. As regards his professional activities, he published several papers on various subjects, including meningococcal meningitis, *x*-ray diagnosis of pulmonary tuberculosis, and tuberculosis in childhood. He was an example of the best type of medical superintendent, taking an active part in every phase of hospital life. It was almost solely owing to his efforts that the hospital kept a cricket side going for many years. He was well loved and respected by his patients, in whose after-careers he took great interest. Many past patients owed their start in a job or career to his personal efforts. He was unsparing of himself in his efforts to help others, and all who worked with him in whatever capacity were sure of his loyalty and of help and support in any worth-while project.

C. G. L. writes: May I add a little flesh to the bare bones of the list of his appointments in your obituary notice (September 6, p. 567) of my old friend Dr. A. E. LARKING? He was a man of irrepressible vitality, and in the village of his retirement was known as a great character, always ready to argue with anyone and put them right on any subject under the sun, to take endless trouble to help them, or to go shooting or fishing with them. Every eye lit up at his approach, often at the prospect of combat. In the first world war the mess that was blessed with his presence was never dull. I remember that when he went it was as though the Public Prosecutor, the Court Jester, the Organizer of Expeditions, and the Public Executioner, all the more dynamic characters of our little Gilbertian Court, had gone too, and

the next scene was flat. He came from farming stock and loved the land, and showed the exuberance and originality of the first generation away from it. The notably good, kind, noble, and clever have their biographers, but I am not sure that we should not be even more grateful to the small class to which Larking conspicuously belonged—the animating. At any rate we miss them as much, or more.

Dr. ROBERT GODWIN CHASE, who died at Brampton, Cumberland, on August 6 at the age of 68, was born at Ashley, near Market Harborough, on August 28, 1883, and was educated at Kibworth grammar school, from which he won a scholarship to Oundle, then under the headmastership of the famous Dr. Sanderson, for whom Chase had a profound admiration. While at Oundle, Chase was captain of cricket, rugby, and fives, and was a prefect and head of his house. From Oundle he went to Trinity College, Cambridge, with an exhibition, and obtained a first class in the Natural Sciences Tripos in his second year. He received his clinical training at Guy's Hospital, where he held various appointments, including that of house-surgeon to Mr. R. P. Rowlands. He qualified M.R.C.S., L.R.C.P. in 1907, and took the M.B., B.Chir. degrees in the following year. While at Guy's he won the Treasurer's Prize for an essay on the diagnosis of acute abdominal conditions. After leaving hospital he practised successively at Chesterfield and Bourton-on-the-Water, where he was surgeon to the local hospitals, and at Sydenham. He was president of the Sydenham District Medical Society in 1932. In 1934 he joined the regional service of the Ministry of Health, serving for several years in the north-eastern division at Leeds. Chase was on the London Panel Committee for many years. He was chairman of the Lewisham Division of the British Medical Association in 1925–6; a member of the Distribution Committee from 1928 to 1935; the Insurance Acts Committee from 1929 to 1931; and the Ophthalmic Committee and its standing subcommittee in 1930–1. Besides being a keen sportsman Chase was much interested in photography. For the last few years of his life his health was poor, but he bore his infirmities with characteristic stoicism. He was a man of strong and determined character, with a tendency to dogmatism, but a sound clinician who to the last maintained his interest in medical science. As a colleague he was loyal and as a friend he was one to be trusted. All who knew him held him in high esteem.—A. R. R.

We record with regret the death in Edinburgh (resulting from an accident) of Dr. WILLIAM JOSEPH MALONEY, consulting neurologist to the City Hospital, New York. William Joseph Maloney was born in Edinburgh on October 16, 1882. He had a brilliant career as a student at Edinburgh University, winning the Houldsworth, Ettles, James Scott, and McCosh Scholarships. After graduating M.B., Ch.B. with first-class honours in 1905 he worked as a senior resident in several well-known Scottish and English hospitals, including the Hospital for Sick Children and the National Hospital for the Paralysed and Epileptic, and then continued his studies abroad in Paris and Munich. He proceeded M.D. in 1907 and was elected a Fellow of the Royal Society of Edinburgh in 1912. In 1911, after he had held a research post at the Crichton Royal Institution, he went to New York, where he became well known as a neurologist and as a leading member of Irish-American circles. One of the appointments he held was the chair of nervous and mental diseases at Fordham University, which awarded him the degree of LL.D. in 1922. He was also on the staff of the Postgraduate Hospital Medical School, New York. At the outbreak of the first world war he immediately joined the R.A.M.C. He served in France and Gallipoli with great gallantry, being twice mentioned in dispatches and winning the Military Cross. He was invalided out of the Army in 1916 as a result of wounds. For a short time after returning to New York he served as a medical recruiting officer for the British Army, but he gave up this post because of his sympathies with the Sinn Fein movement in Ireland. Later he attained some notoriety as the author of a pamphlet entitled *The Reconquest of America*, which he wrote as a skit on British propaganda. Apparently this was taken seriously by some officials in the U.S.A. and described as "an amazing British secret service document." During the early part of his career Maloney published many papers on neurological and other subjects, and he wrote a book on *Locomotor Ataxia*, which was published in 1918.

Medico-Legal

NOT A "HOSPITAL" WITHIN THE ACT

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

By his will Mr. H. A. Couchman, who died on January 9, 1941, left a legacy of £100 and a share of his residuary estate to the Leominster Orthopaedic Clinic. The clinic, which before 1948 was a voluntary institution first affiliated to and later a unit of the Herefordshire branch of the British Red Cross Society, provides aftercare treatment in a hut belonging to the Red Cross in the grounds of the Leominster Cottage Hospital. Since July, 1948, the work of the clinic has been carried on under the Robert Jones and Agnes Hunt Orthopaedic Hospital Management Committee. The funds due under the will were claimed by the Herefordshire branch of the British Red Cross Society and by the hospital management committee, and accordingly the trustees of the will took out a summons in the Chancery Division of the High Court asking to whom they should be paid.

Mr. Justice Danckwerts decided[1] that the bequest was not a gift to the Red Cross branch, but a gift for the charitable purposes described in the will—namely, the purposes of the clinic. He also decided against the management committee's claim under the provisions of section 60 of the Act, on the ground that the clinic was not a "hospital" as defined by section 79 of the Act—that is, "any institution for the reception and treatment of persons suffering from illness or mental defectiveness . . . and includes clinics . . . maintained in connexion with any such institution. . . ." In his lordship's view "reception" in the section meant taking people into a building and keeping them there, as was done in the ordinary case of reception into hospital. Accordingly he came to the conclusion that this particular institution was not for the reception and treatment of persons within the meaning of the definition section of the Act, nor was it maintained in connexion with a particular hospital. He directed that the charitable purposes of the bequest should be carried out by a scheme which in the circumstances should be administered by the hospital management committee.

[1] *The Times*, February 6.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

The following have been reappointed Associate Lecturers in the Faculty of Medicine for three years from January 1, 1953, in the subjects indicated: *Physic*, L. B. Cole, M.D., F.R.C.P., L. C. Martin, M.D., F.R.C.P., and A. P. Dick, M.D., M.R.C.P. *Surgery*, P. H. R. Ghey, M.Chir, F.R.C.S., V. C. Pennell, M.B., B.Chir., F.R.C.S., and B. McN. Truscott, M.B., B.S., F.R.C.S. *Orthopaedic Surgery*, R. W. Butler, M.D., M.Chir., F.R.C.S., and T. J. Fairbank, M.B., B.Chir., F.R.C.S. *Otolaryngology*, A. S. H. Walford, M.B., B.Chir., F.R.C.S., and K. F. Wilsdon, B.M., B.Ch., F.R.C.S.Ed. *Ophthalmology*, E. G. Recordon, M.D., and G. F. Wright, M.B., B.Chir., D.O.M.S. *Obstetrics and Gynaecology*, O. Lloyd, M.D., F.R.C.S., M.R.C.O.G., and Janet E. Bottomley, M.D., F.R.C.S., M.R.C.O.G. *Paediatrics*, D. M. T. Gairdner, D.M., M.R.C.P. *Dermatology*, C. H. Whittle, M.D., F.R.C.P. *Psychiatry*, E. B. Davies, M.D., D.P.M., and R. A. Noble, M.B., Ch.M., M.R.C.P., D.P.M. *Radiology*, F. R. Berridge, M.B., B.Chir., D.M.R.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **August 23** (No. 34) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire	1951 Eng. & Wales	1951 Lond.	1951 Scot.	1951 N. Ire.	1951 Eire
Diphtheria	23	5	6	1	2	23	2	8		0
Dysentery	119	26	81	1	1	174	43	54	4	
Encephalitis, acute	3	0	1	0	1	5	2	1	0	
Enteric fever:										
Typhoid	13	0	0	0	1	6	0	1	0	1
Paratyphoid	58	0	2(B)	2		46	4	1(B)	9	
Food-poisoning	190	16		1		128	17		2	
Infective enteritis or diarrhoea under 2 years				20	39				9	79
Measles*	5,256	573	25	22	61	2,352	51	62	106	64
Meningococcal infection	29	3	13	1		31	2	9	1	3
Ophthalmia neonatorum	39	4	8	0	2	40	1	4	0	1
Pneumonia†	207	13	115	4	1	181	12	88	2	•
Poliomyelitis, acute:										
Paralytic	152	12	11	9	3	60	3	17	5	2
Non-paralytic	68	4				56	1			
Puerperal fever§	244	33	10	1		240	32	8	1	2
Scarlet fever	559	43	139	12	30	436	29	120	5	27
Tuberculosis:										
Respiratory			137	29				140	21	
Non-respiratory			30	5				22	5	
Whooping-cough	1,800	75	123	46	112	2,948	134	307	45	132

DEATHS in Great Towns	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire	1951 Eng. & Wales	1951 Lond.	1951 Scot.	1951 N. Ire.	1951 Eire
Diphtheria	0	0		0		*0*	0	*0*	0	0
Dysentery	0	0		0			0		0	
Encephalitis, acute		0					0			0
Enteric fever	0	0		0						
Infective enteritis or diarrhoea under 2 years	2	0	0	1		*7*		*1*	1	0
Influenza	5	1		0		*2*	0	*0*	0	0
Measles		0	1	0			0	*0*	0	0
Meningococcal infection		1					0	*0*		
Pneumonia	99	9		6		*117*	13		8	1
Poliomyelitis, acute	8	2				*2*	0			0
Scarlet fever		0		0			0	*0*	0	0
Tuberculosis:										
Respiratory	83	9	12	3		*133*	13	*12*	3	9
Non-respiratory		3	1	2			5	*3*	1	3
Whooping-cough	1	0		0		*1*	0	*0*	0	0
Deaths 0–1 year	189	25	31	8	—	*208*	33	*29*	7	10
Deaths (excluding stillbirths)	3,953	585	486	94		*3,992*	632	*496*	96	136
LIVE BIRTHS	7,194	1074	807	207		*6,751*	1119	*858*	195	419
STILLBIRTHS	170	23	32			*170*	26	*20*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Poliomyelitis

Poliomyelitis notifications (uncorrected) in the week ending August 30 (35th week of the year) were as follows: paralytic 150 (152), non-paralytic 65 (68); total 215 (220). This is a decrease of 5 compared with the previous week, the figures for which are in parentheses. Up to and including the week ending August 30 the overall uncorrected notification rate for England and Wales was 5.9 per 100,000.

Infectious Diseases

Infectious diseases were less prevalent during the week ending August 23 in England and Wales, and decreases were recorded in the number of notifications of measles 843, scarlet fever 84, whooping-cough 72, and acute poliomyelitis 38.

The decline in the incidence of measles was mainly due to falls in a few counties; the largest were London 178, Lancashire 154, Essex 116, and Yorkshire West Riding 108. Only small variations were reported in the local trends of scarlet fever. The largest fluctuations in the trends of whooping-cough were decreases in notifications in Staffordshire 56 and Lancashire 43. The number of notifications of diphtheria was 6 more than in the preceding week; the chief features of the local returns were increases of 3 in London and Lancashire.

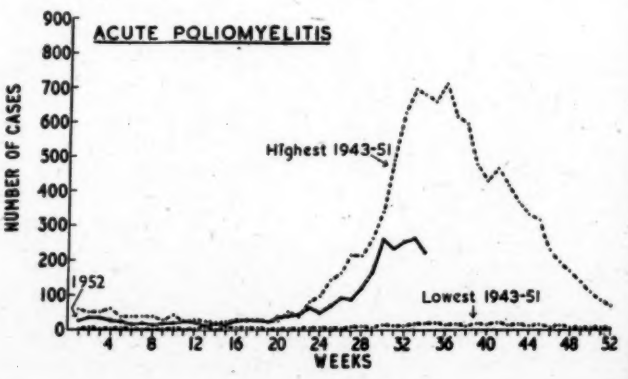
The number of notifications of paratyphoid fever was 18 more and of typhoid fever 9 more than in the preceding week. The rise in the incidence of paratyphoid fever was due to an increase in Wales (Monmouthshire 17 and Glamorganshire 12). The largest returns of paratyphoid fever during the week were Glamorganshire 21 (Port Talbot M.B. 6) and Monmouthshire 21 (Mynyddislwyn U.D. 8).

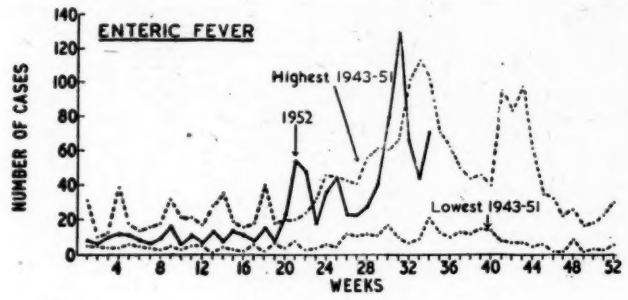
The number of notifications of acute poliomyelitis was 18 less for paralytic and 20 less for non-paralytic cases than in the preceding week. The largest returns during the week were Yorkshire West Riding 40 (Leeds C.B. 10, Sheffield C.B. 6, York C.B. 6); London 16; Lancashire 16 (Liverpool C.B. 6); Essex 12 (Southend-on-Sea C.B. 6); Durham 11 (Stanley U.D. 4).

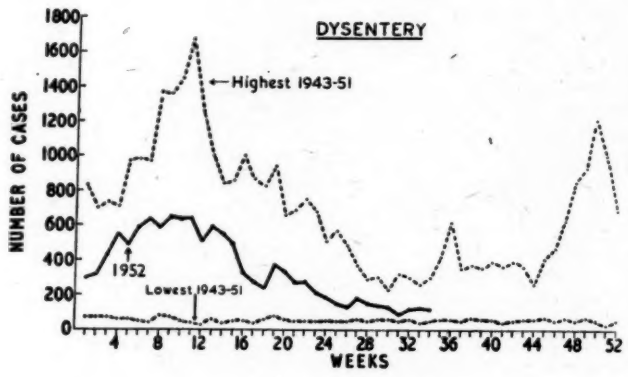
The number of notifications of dysentery was 6 less than in the preceding week. The largest centres of infection were London 26; Middlesex 20; Essex 14 (Southend-on-Sea C.B. 14); Lancashire 11.

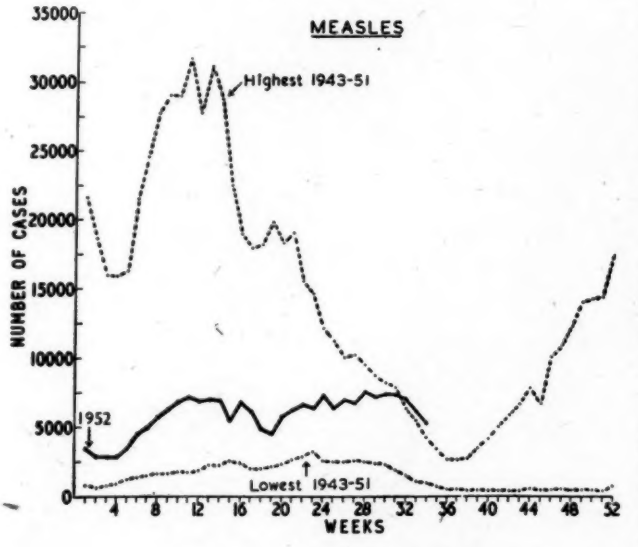
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1943–51 are shown thus - - - - - - - -, the figures for 1952 thus ————. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Poliomyelitis in the Rhineland

According to a report in the *Manchester Guardian* (September 3) 360 new cases of poliomyelitis were notified in the Rhineland during the first week of August. There was a drop in notifications during the second week, but the figure for the third week rose again to 332. It is thought that the wet and close weather which has recently been experienced is likely to favour the spread of the epidemic. The public health authorities have now forbidden bathing in streams or unchlorinated swimming-baths. Children are not to be allowed to visit fairs or to camp under canvas.

Post-infectious Encephalitis

In the August issue of the *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service* Dr. E. T. Conybeare analyses the number of cases of post-infectious encephalitis notified during 1951. A total of 119 cases was notified during the year, and it was possible to obtain further information about 114 of these cases from medical officers of health. In four of the notified cases the diagnosis was subsequently changed to polio-encephalitis and in a further 19 the diagnosis of encephalitis was believed to be mistaken and the notification was withdrawn. Out of the 91 cases remaining, 37 were associated with mumps, 32 (4 deaths) with measles, 9 with chicken-pox, 4 (2 deaths) with influenza, 2 with vaccinia, 2 with rubella, 2 with herpes, 2 with whooping-cough, and 1 with scarlet fever. Post-measles encephalitis was notified twice as often during 1951 as in 1950, and post-mumps encephalitis three times as often. The rise in the notifications of post-measles encephalitis was proportionate to the rise in the notifications of measles, which in 1951 were nearly double the 1950 figure.

Week Ending August 30

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 557, whooping-cough 1,861, diphtheria 22, measles 3,649, acute poliomyelitis 215, dysentery 90, paratyphoid fever 44, and typhoid fever 4.

Medical News

British Association Meeting.—Belfast is proving as attractive to members of the British Association as Dublin did to doctors two months ago: by the start of the meeting the record number of 4,350 scientists had registered, a figure exceeded only at the centenary assembly in London in 1931. The Duke of Edinburgh, the Association's immediate past-president, presented prizes on the first day, and later went to the inaugural meeting. At this, in his presidential address, Professor A. V. Hill, F.R.S., took up the Duke's challenge to scientists to consider how their discoveries could be kept for man's benefit and not used for his destruction. Professor Hill chose as his subject "The Ethical Dilemma of Modern Science." At a council meeting Sir Edward Appleton, F.R.S., was elected president for 1953, when the Association will meet at Liverpool. Sir Edward is Principal and Vice-Chancellor of Edinburgh University, and was formerly Secretary of the Department for Scientific and Industrial Research. An account of the medical aspects of this year's meeting of the British Association will be published in the *Journal*.

European Cardiologists in Congress.—The first congress of the European Society of Cardiology was held in London this week, under the auspices of the British Cardiac Society. The European Society owes its origin to the enthusiasm of Belgian cardiologists. In 1948 the Belgian Society of Cardiologists invited representatives of all European cardiological societies to Brussels early in 1949 to discuss the project. As a result of this meeting the formation of the European Society was proceeded with, Professor Charles Laubry (Paris) being elected honorary president and Professor Gustav Nylin (Stockholm) president. Membership is limited to members of national cardiological societies. Sir John Parkinson was appointed chairman of the London congress. At the scientific sessions of the congress, which were held in the halls of London University, nearly 100 papers were presented, and in addition there was a symposium on the surgical treatment of mitral stenosis. The principal social entertainments were an official banquet at Grosvenor House, receptions at the Royal College of Physicians, University of London, British Council, and Ciba Foundation, and a garden party given by Sir John and Lady Parkinson at their home in Hampstead.

Too Few Dentists.—According to Mr. C. G. Spiridion, president of the British Dental Association, the dental condition of a large proportion of the people of Britain is appalling. He said that this would not be remedied unless the number of dental practitioners was increased. At present there were 15,000 dentists on the register, representing one dentist to every 3,333 of the population. This figure

compared with a ratio of 1 to 2,163 in Scandinavia. Mr. Spiridion was speaking at the 72nd annual conference of the British Dental Association at Cardiff last week.

Labels for Dangerous Chemicals.—Each year numbers of chemical workers are injured and killed because the containers they handle are inadequately labelled. Sometimes there is no label, sometimes it is inaccurate, and sometimes the worker cannot read the label. To prevent these accidents the International Labour Office has put forward proposals for a world-wide system of labelling dangerous substances. The suggested labels consist of warning signs on white and orange rectangles—an exploding grenade for explosives, a lighted match for inflammable substances, a skull for toxic substances, a corroded hand for corrosives, and a skull and crossbones against a radiant "R" for radioactive materials. These suggestions are now being considered by the I.L.O. Chemical Industries Committee.

T.U.C. on Germ Warfare.—By a narrow majority, and after opposition from the general council, the Trades Union Congress passed a resolution condemning the use of "bacteriological weapons." The resolution, which was moved by Dr. P. W. Brian, of the Association of Scientific Workers, urges "the Government, through the United Nations, to secure a new international agreement prohibiting their use." Opposition to the resolution was on account of the assumptions behind it, but the mover denied that its acceptance involved any secondary considerations.

Pay at Broadmoor.—In a speech at Nottingham on September 3 the Minister of Health, Mr. Iain Macleod, said that he was fully alive to the need to review the pay of the staffs of the three State institutions, Broadmoor, Rampton, and Moss Side. Although these institutions are "hospitals" in the National Health Service, most of their staffs belong to the Prison Officers Association. Rampton and Moss Side are used for the detention of dangerous certified mental defectives, many of whom have not been convicted of offences in court but have proved unmanageable in ordinary mental hospitals or elsewhere; these defectives can be discharged on medical authority alone, but release from Broadmoor requires the sanction of the Home Secretary.

B.M.S.A. London Conference.—Clinical and preclinical students from nearly every university in Britain have been attending the British Medical Students Association's conference in London this week. The conference was opened by Sir Cecil Wakeley, P.R.C.S., and the programme included visits to teaching hospitals in London, to the Maudsley Hospital, and to the maxillo-facial unit at East Grinstead. The conference closes to-day with a talk by Dr. Charles Hill, Parliamentary Secretary to the Ministry of Food.

Dollar Grant for Tuberculosis Research.—University College, Dublin, has received a grant of $30,000 from the Lasdon Foundation, New York, for research on the chemotherapy of tuberculosis. The work will be carried out at the Irish Medical Research Council's laboratories at Trinity College, Dublin, under the direction of Dr. Vincent C. Barry. The Lasdon Foundation was established by Mr. William S. Lasdon, president of the Nepera Chemical Co., to subsidize medical research in all parts of the world.

Pakistani Doctors in Britain.—A United Kingdom branch of the Pakistan Medical Association has been formed in London. The president is Dr. S. D. Jouhar and the secretary-treasurer Dr. M. Shaffi. Further information may be obtained from Dr. Shaffi at 19, Bernard Street, London, W.C.1.

Poliomyelitis in Canada.—In the Western provinces of Canada there have been 1,300 cases of poliomyelitis this year, 88 being fatal. This is the worst outbreak there for many years.

Guest Professor.—Professor Earl R. Loew, Professor of Physiology in Boston University School of Medicine, has taken up his appointment as Guest Professor in the department of pharmacology and therapeutics, St. Andrews University Medical School, Dundee. Professor Loew will be in Dundee for the month of September.

Dr. A. S. Parkes, F.R.S., head of the division of experimental biology of the National Institute for Medical Research, Mill Hill, is leaving for a 10-week lecture tour of Latin America on September 17. The tour has been arranged by the British Council. Dr. Parkes will visit Brazil, Uruguay, Argentina, and Chile.

NEW ISSUES

Thorax.—The next issue of this journal (Vol. 7, No. 3) will be available in a week's time. The principal contents will include:

CARDIAC ARREST AND VENTRICULAR FIBRILLATION. I. K. R. McMillan, F. B. Cockett, and P. Styles.

A STUDY OF THE PATHOLOGY AND PATHOGENESIS OF BRONCHIECTASIS. F. Whitwell.

CARCINOMA OF THE MIDDLE LOBE. P. E. Baldry.

AN ABNORMAL DISPOSITION OF THE PULMONARY VEIN. H. Butler.

THE EFFECT OF THE RATE OF BREATHING ON THE MAXIMUM BREATHING CAPACITY DETERMINED WITH A NEW SPIROMETER. L. Bernstein, J. L. D'Silva, and D. Mendel.

A CASE OF THROMBUS IN THE LEFT AURICLE SIMULATING MITRAL STENOSIS. Eric M. Nanson and R. Milnes Walker.

A CASE OF BILATERAL PARASTERNAL DIAPHRAGMATIC HERNIA. R. Warwick-Brown.

THE BLOOD SUPPLY OF THE LUNG IN PULMONARY TUBERCULOSIS. Leon Cudkowicz.

Issued quarterly; annual subscription £2 2s., single copy 12s. 6d.

British Journal of Pharmacology and Chemotherapy.—The September issue of this journal (Vol. 7, No. 3) is now available. The principal contents include:

RENAL FUNCTION IN LEAD POISONING. A. Ursula Pardoe.

THE UPTAKE AND EXCRETION OF WATER IN RATS POISONED WITH LEAD. A. Ursula Pardoe and Miles Weatherall.

THE BIOLOGICAL BEHAVIOUR OF A NEW SYNTHETIC ANTICOAGULANT (DEXTRAN SULPHATE) POSSESSING HEPARIN-LIKE PROPERTIES. K. W. Walton.

THE EFFECT OF CHAIN-LENGTH ON CURARIZING POTENCY IN THREE HOMOLOGOUS SERIES. H. O. J. Collier.

THE PHARMACOLOGICAL PROPERTIES OF "LAUDOLISSIN"—A LONG-ACTING CURARIZING AGENT. H. O. J. Collier and Barbara Macauley.

EVALUATION OF TWO SYNTHETIC CURARIZING AGENTS IN CONSCIOUS VOLUNTEERS. Richard I. Bodman.

INFLUENCE OF CHAIN-LENGTH UPON SOME PHARMACOLOGICAL PROPERTIES OF S-ALKYL ISOTHIOUREAS. F. N. Fastier and C. S. W. Reid.

A METHOD FOR TESTING ANALGESICS IN MICE. R. Singh Grewal.

SOME PROPERTIES OF NISIN. J. L. Gowans, N. Smith, and H. W. Florey.

THE NATURE OF THE PULMONARY RECEPTORS EXCITED BY ANTIHISTAMINES. J. V. Jones.

THE PREVENTION OF ENCEPHALITIS DUE TO THE VIRUSES OF EASTERN EQUINE ENCEPHALOMYELITIS AND LOUPING-ILL: EXPERIMENTS WITH TRYPAN RED, MEPACRINE, AND MANY OTHER SUBSTANCES. E. Weston Hurst, P. Melvin, and J. M. Peters.

THE ACTION OF MEPACRINE AND TRYPAN RED IN A NUMBER OF VIRUS DISEASES. E. Weston Hurst, J. M. Peters, and P. Melvin.

PHARMACOLOGICAL ACTIONS OF INJECTED CHOLINESTERASE. I. T. Beck.

SYNTHETIC AMOEBICIDES: PART I. ANTHRAPYRIMIDINES. W. R. Jones, J. K. Landquist, and N. Senior.

THE ANTIFILARIAL ACTION AND TOXICITY OF METHYLENE VIOLET AND OF OTHER COMPOUNDS OF THE PHENOSAFRANINE SERIES. F. Hawking, W. E. Ormerod, J. P. Thurston, and W. A. F. Webber.

Issued quarterly; annual subscription £4 4s., single copy £1 5s.

These journals are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

COMING EVENTS

Congress of Internal Medicine.—The Second International Congress of Internal Medicine opens in London on September 15, under the patronage of the Queen. The congress has been organized by the International Society of Internal Medicine. The congress president is Sir Russell Brain. All meetings will be held at Friends House, Euston Road, London, N.W.1. At the opening session at 11 a.m. on September 15 the Minister of Health, Mr. Iain Macleod, will welcome members of the congress. The scientific sessions consist of symposia on important topical subjects, opened in each case by three or four recognized authorities and followed by a general discussion. The subjects of the symposia are: "The sprue syndrome: idiopathic steatorrhoea and coeliac disease" (2 to 5 p.m. on September 15; chairman, Dr. Nanna Svartz, Stockholm); "The clinical importance of disturbances of fluid and electrolyte balance" (9.30 a.m. to 12.30 p.m. and 2 to 5 p.m. on September 16; chairman, Sir Harold Himsworth, London); "Some aspects of neurotropic virus disease" (9.30 a.m. to 12.30 p.m. on September 17; chairman, Sir Russell Brain, London); "Antibiotics in man" (2 to 5 p.m. on September 17; chairman, Sir Lionel Whitby, Cambridge). On September 18 visits to leading London hospitals have been arranged. Official functions include a Government reception at Church House, Westminster, a reception at the Royal College of Physicians, and a banquet at the Mansion House. Further details may be obtained from the headquarters of the congress at Friends House (tel. Euston 1091 and 1092).

Children and Young Animals.—An unusual course of postgraduate lectures has been arranged for the coming session at the Institute of Child Health, Great Ormond Street. The idea is to compare disease in the young animal with that in the child. Most of the lecturers are distinguished veterinary workers. Subjects covered include comparative physiology and pathology, genetics, epidemiology, prenatal and neonatal disease, deficiency diseases, inborn errors of metabolism, and virus diseases. Ten lectures will be given, at weekly intervals, starting on October 13. The fee for the course is £2 2s., and for a single lecture 5s. Application for admission should be made to the Secretary, Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Wednesday, September 17

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—5.30 p.m., Clinical Society Meeting. "*Keratome and Scissors for Cataract Incision*," by Mr. Howard Reed.

Friday, September 19

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, University of Glasgow, 11 a.m. Scientific papers (see also September 20).

Saturday, September 20

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, University of Glasgow, 11 a.m. Scientific papers (see also September 19).

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, London, W.C.—11 a.m., "*Recent Research in Otology*," by Dr. Stacey R. Guild (Baltimore, U.S.A.).

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Clarke.—On August 29, 1952, at the Purey Cust Nursing Home, York, to Catherine (formerly Waugh), wife of Mr. P. R. R. Clarke, F.R.C.S., a son.

Hill.—On August 21, 1952, at Robinson Memorial Hospital, Ballymoney, Northern Ireland, to Nancy (formerly Hinchcliff), wife of Dr. William J. C. Hill of Duncreggan, Portrush, Northern Ireland, a daughter—Alison Mary.

Johnson.—On August 15, 1952, at Kuala Belait Hospital, Brunei, Borneo, to Betty Jane (formerly Powell), wife of Dr. Austin Johnson, a second son.

Tasker.—On July 25, 1952, at Northampton, to Anita, wife of Dr. J. R. Tasker, a son.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

When Should Duodenal Ulcers be Treated Surgically?

Q.—*For how long is it worth persevering with the medical treatment of a duodenal ulcer before recommending surgery?*

A.—There is no hard-and-fast line between medical and surgical treatment for uncomplicated duodenal ulcer, and a decision can be arrived at only after consideration of many relevant factors, such as the age, length of history, opportunities for pursuing a convalescent ulcer regime, persistence of symptoms or radiological evidence of ulceration, frequency of relapses, associated medical complications, and availability of surgical skill.

The natural history of duodenal ulcer would appear to be a series of ulcers which come and heal with appreciably long remissions between them, but in due course healing no longer occurs and a persistent chronic ulcer crater is found. Pain, however, does not necessarily continue, but the remissions are shorter. It is at this stage, when there is a persistent ulcer crater which can be demonstrated radiologically during pain-free intervals, that surgery should be seriously considered. In the early phases of the evolution of the condition operation may be needed to save the patient's job rather than his life, when recurrences have undermined his efficiency and threatened his livelihood. It may sound an unsympathetic approach, but in general terms the patient should earn his gastrectomy. With our present state of knowledge we are not justified in recommending operation in young patients with short histories and until the patient has had several troublesome relapses adequately treated medically, or complications. In the older age groups one is justified in operating earlier in view of the greater risk of complications.

Although some 80% of patients do very well after partial gastrectomy it must be remembered that a proportion suffer from various degrees of abdominal discomfort, inability to regain their weight, sense of general fatigue, and a greater liability to tuberculosis. Women certainly do less well than men. Until we have a clear-cut picture of the 10-, 15-, and 20-year follow-up results of gastrectomy one is justified in pursuing a cautious surgical approach and reserving the operation for those who are becoming crippled by their disability.

Test of Cure in Brucellosis

Q.—*A woman of 55 has now had two bouts of brucellosis (antibody titre of 1:5,000 to Br. abortus), treated with chloramphenicol. What is the likelihood of further attacks, and what test of cure is advised?*

A.—The likelihood of a further recurrence cannot be estimated without knowing whether chloramphenicol was given in adequate dosage (at least 2 g. daily) and for an adequate period (at least 10 days). The frequency of recurrence after an adequate first course is about 60%, after a second very much less. It should be added that this frequency is about the same for all three appropriate antibiotics, chloramphenicol, aureomycin, and terramycin, but, in view of recent reports of dangerous toxic effects from chloramphenicol, it might be advisable to conduct any further treatment, if necessary, with one of the others.

The best assurance of cure is a normal temperature continued for a number of weeks, but if laboratory tests are to be applied those available are cultures from the blood, cerebrospinal fluid, and bone marrow, and repeated agglutination tests which show a slow but progressive fall when the infection has been eliminated.

Progression of Hay-fever to Asthma

Q.—*What is the evidence that the administration of antihistamine drugs for hay-fever predisposes to the later development of asthma?*

A.—According to the world literature, the natural history of between 50 and 75% of cases of hay-fever untreated by desensitization is for them to progress to asthma. However, this change occurs slowly, usually after only 10 to 20 seasons of hay-fever. In the experience of a number of allergists when only antihistamine drugs have been given an even greater percentage of cases become asthmatic. The evidence for this is purely clinical, as a satisfactorily controlled experiment has not proved possible. There seems little doubt that the percentage of hay-fever cases progressing to asthma has increased considerably in recent years, but other factors, such as the stress and strain and frustration of the post-war period, may partly account for this.

A "Blackout"?

Q.—*In criminal cases the accused sometimes says that he had a blackout at the material time. What exactly is a blackout? Is there such a condition apart from that affecting airmen at very high altitudes? Many patients are convinced that they suffer from blackouts.*

A.—Apart from the condition mentioned in the question, the word "blackout" has no specific medical meaning. Patients frequently use the term in describing their symptoms, and in the writer's experience the actual disability has been very diverse, including all forms of epilepsy, status epilepticus, syncope, spontaneous hypoglycaemia, concussion, the aura of migraine, aural vertigo, hysterical fugues, and vague feelings of anxiety. It is essential to get an adequate history from the individual to discover what he means by a blackout, and if possible to obtain a reliable account from an observer of the incident before a diagnosis can be made.

Salt in Pregnancy

Q.—*Can you tell me what is the teaching about the use of salt in pregnancy? In India in certain months native teaching is against it. In Australia, among the aborigines, the men make long journeys to get it for expectant mothers.*

A.—Pregnancy is normally accompanied by some retention of sodium and water in the tissues, and this is thought to be an effect of steroid hormones coming from the placenta or the adrenal or both. Pre-eclampsia and eclampsia are characterized by an abnormal increase in the retention of these substances. Pregnant women vary in their tolerance to sodium, and some, presumably those with some sort of predisposition to pre-eclampsia, react by oedema and hypertension. All manner of experiments are at present being carried out to determine the relation of sodium intake and adrenal and placental function to toxaemia of pregnancy, but the situation is still too complex and nebulous to allow any firm teaching about salt in the diet during pregnancy. Presumably sodium chloride in reasonable amounts is harmless to most pregnant women. If, however, they have a predisposition to eclampsia, or if they are already suffering from pre-eclampsia, its administration in large amounts can cause fits and coma. It is usual, therefore, to restrict the intake of sodium chloride in women with pre-eclampsia.

Customs among different native races may be influenced to some extent by climate. Indeed, it has already been suggested that waves in the incidence of eclampsia which appear to coincide with extreme heat or cold are determined, in part at least, by consequent alterations in salt and water intake and excretion.

The whole subject is complicated, and the inquirer might like to consult W. J. Dieckmann's recent articles in *Toxaemias of Pregnancy, Human and Veterinary* (J. and A. Churchill, Ltd., 1950) and the *American Journal of Obstetrics and Gynecology*, 1952, **63**, 783.

NOTES AND COMMENTS

Coeliac Disease and Cereals.—Professor J. M. SMELLIE and Dr. CHARLOTTE M. ANDERSON (Birmingham) write: Your reply ("Any Questions?" July 19, p. 173) may be a little ambiguous to those who are not in touch with recent developments, and the following dietetic details may be helpful. As far as our experience in Birmingham goes, only the gluten from wheat and rye need be excluded from the diet of these children. Oats has been given in reasonable quantities and did not appear to have any deleterious influence on the disease, but further studies are being pursued. It is only exceptionally that we have to restrict the fat intake. Experience has demonstrated that better clinical progress is obtained when a diet containing normal amounts of fat, as well as protein and carbohydrate, is offered from the outset of treatment. If a child has been treated previously with a low fat diet it may be necessary to increase fat cautiously, but even in such cases a full fat intake (40–50 g.) can usually be tolerated within two to three weeks. Thus the following foods may be given: All meats, cheese, eggs, milk (about 1 pint—568 ml.—a day), vegetables, potatoes, rice, jam, honey, jellies, butter, margarine. For cereals—corn flakes or rice krispies. So far only Quick Quaker oats have been used for porridge making. The child may have any beverage, including tea, coffee, cocoa, or drinking chocolate. Ice-cream should be made at home, as some commercial brands do contain flour. The following articles of food should not be given: Bread, biscuits, pastry, cakes, cereals made from wheat, semolina, vermicelli, macaroni, rye biscuits, rye-bread, puddings containing flour or bread, soup, gravies or sauce mixed with flour. *The following is an example of a wheat-flour-free diet.—Breakfast:* Cornflakes, rice krispies, or porridge. Sugar. Cow's milk. Boiled or poached egg, bacon and tomato. Wheat-starch biscuits, soya biscuits, corn-flour biscuits, or wheat-starch loaf. Butter, jam, etc. *Dinner:* Average portion of meat, chicken, fish. Spinach, cauliflower, cabbage, or carrots. Potatoes, boiled, baked, or fried. Rice pudding, corn-flour blancmange, junket, jelly, stewed fruit. *Tea:* Milk or weak tea to drink. Jelly, fruit, tomato, honey, jam, syrup. Wheat-starch biscuits, corn-flour biscuits, wheat-starch loaf or cakes (from given recipes). Butter. *Supper:* Milk. Egg custard, fruit purée, or grated cheese and salad. Wheat-starch, corn-flour, or soya biscuits.

Miss MARGARET E. WRIGHT and Miss M. E. AITKEN (King's College Hospital) write: It is possible to produce a gluten-free yeast loaf which has a bread-like texture and flavour and has proved more acceptable to patients than pure-starch scones and buns, particularly with savoury food such as egg at breakfast, etc. Its keeping time is about two days in an airtight tin. 12 oz. wheat starch, ¼ oz. cooking fat, 1 oz. yeast started with 1 teaspoonful sugar, 1 teaspoonful salt, and 12 oz. lukewarm water and milk mixed. Add the salt to the wheat starch and rub in the fat. Mix the creamed yeast and sugar with the milk and water, and stir into the starch thoroughly, seeing that no lumps are left. Allow the mixture to stand in a warm place for 20 minutes exactly. Pour the batter into 2-lb.-size bread tins previously warmed and greased. Bake at regulo 5 for 15 minutes, then turn up the gas to regulo 7 (400° F.); leave for 5 minutes. Take the loaves out of the tins, turn upside down on the oven shelf, and continue cooking for 15 more minutes. We hope this recipe may be of use to those who are concerned with the dietetic treatment of coeliacs.

Electric Fences.—A medical farmer writes: As a user of extensive electric fencing ("Any Questions?" August 30, p. 523) for controlling the perambulation of brood sows at pasture, I endorse what you say about the harmlessness of the current. Indeed, the difficulty is to keep the live wire free from contact with long grasses and bents, which, especially in damp weather, earth the currents and thereby diminish the degree of shock, which then becomes infinitesimal, if not imperceptible.

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